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Analysis of Algorithms Predicting Blood: Air and Tissue: Blood Partition Coefficients from Solvent Partition Coefficients for use in Complex Mixture Physiological Based Pharmacokinetic/Pharmacodynamic Modeling

Teresa R. Sterner

OPERATIONAL TECHNOLOGIES CORP.
1370 N. FAIRFIELD ROAD, SUITE A
BEAVERCREEK, OH 45432

Peter J. Robinson

MANTECH GEO-CENTERS JOINT VENTURE
P.O. BOX 31009
DAYTON, OH 45437-0009

David R. Mattie

OPERATIONAL TOXICOLOGY BRANCH
HUMAN EFFECTIVENESS DIRECTORATE
AIR FORCE RESEARCH LABORATORY
WRIGHT-PATTERSON AFB, OH 45433-7400

G. Allen Burton

WRIGHT STATE UNIVERSITY
DAYTON, OH

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Human Effectiveness Directorate
Biosciences and Protection Branch
Applied Toxicology Branch
Wright-Patterson AFB OH 45433-7400

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This technical report has been reviewed and is approved for publication.

FOR THE DIRECTOR

//SIGNED//

MARK M. HOFFMAN
Deputy Chief, Biosciences and Protection Division
Air Force Research Laboratory

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*Sterner, Teresa R.; **Robinson, Peter J.; ***Matie, David R.;****Burton, G. Allen

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

*Operational Technologies Corp.
1370 N. FairfieldRd, Suite A
Beavercreek, OH 45432

**Mantech Geo-Centers Joint Venture
P.O. Box 31009
Dayton, OH 45437-0009

**** Wright State University Dayton, OH

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13. ABSTRACT *(Maximum 200 words)*

Algorithms predicting tissue and blood partition coefficients (PCs) from solvent properties (octanol:water, saline or water:air, oil:air coefficients) were compared to assess their usefulness for a petroleum mixtures physiologically based pharmacokinetic/pharmacodynamic model. Measured blood:air and tissue:blood PCs were sought from literature resources for 14 JP-8 components. PCs, mainly from vial equilibration experiments, were separated by species (rat and human) and averaged by tissue and chemical. Average experimental PCs were then compared with predicted PCs calculated using algorithms from nine published sources. The algorithms chosen use solvent PCs due to the relative accessibility of these parameters. Tissue:blood PCs were calculated from ratios of predicted tissue:air and experimental blood:air values (PC_{EB}). Calculated PCs were evaluated using percent error compared to the experimental value. Of the 231 calculated values, 29% performed within ± 20% of the experimental PC values. Algorithms were divided into three main types. Empirical equations (derived from linear regression of experimental PC data), physiologically based equations (based on water and lipid components of a tissue type), and hybrid equations (physiological parameters and empirical factors combined) each performed equally well. PC_{EB} values were compared with tissue:blood PCs calculated from ratios of predicted tissue:air and predicted blood:air values (PC_{PB}). Overall, 68% of PC_{EB} values had smaller absolute percent errors than PC_{PB} values. Physiological equations should not be used to calculate PC_{PB} values as 100% of these PC_{PB} values had higher absolute percent errors than corresponding PC_{EB} values. If calculated PC values must be used in models, a comparison of experimental and predicted PCs for chemically similar compounds is advisable, so one understands the expected error level in calculated values.

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PREFACE

This research was accomplished at the Operational Toxicology Branch, Human Effectiveness Directorate of the Air Force Research Laboratory, Wright-Patterson AFB, OH, under Richard R. Stotts, Branch Chief. The contractors were under the direction of Peter Lurker (Operational Technologies Corp., Dayton, OH, Contract # F33601-02-F-A211) and Darol Dodd (ManTech Environmental Technology, Dayton, OH, Contract # F-33615-00-C-6060). This technical report was written for AFRL Workunit 1710D435.

The basis of this work was performed to support development of a JP-8 mixtures model and to fulfill obligations toward a Masters Degree in Environmental Science at Wright State University, Dayton, OH. A synopsis of this work will be presented as a poster at the Society of Toxicology Annual Meeting in Baltimore, MD, in March 2004.

The authors acknowledge the invaluable statistical expertise provided by Chuck Goodyear, consultant, AFRL/HEC, Wright-Patterson AFB, OH.

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LIST OF ACRONYMS

DEET	N,N-diethyl-m-toluamide
g	gram
iv	intravenous
JP-8	jet propulsion fuel number 8
mg	milligram
mL	milliliter
n	number
PBPK	physiologically based pharmacokinetic
PC	partition coefficient
PC_{EB}	partition coefficient calculated using experimental blood:air value
PC_{PB}	partition coefficient calculated using predicted blood:air value
R^2	correlation coefficient

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INTRODUCTION

Jet fuels are complex petroleum based mixtures. Analysis of JP-8 jet fuel by mass spectrometry yields a spectrum of approximately 300 identifiable peaks (Rodgers *et al.*, 1999). U.S. military personnel have been and continue to be exposed frequently to vapor, aerosol and liquid forms of JP-8 since it became the standardized military fuel (Olsen *et al.*, 1998; Kobayashi and Kikukawa, 2000). To make the situation more complicated, military exposures to JP-8 can occur concurrently with exposures to high levels of N,N-diethyl-m-toluamide (the insect repellent DEET), pyridostigmine bromide (anti-nerve gas agent) and permethrin (pesticide), which may be used during deployment. Concurrent military occupational exposures have been implicated in Gulf War Syndrome (Peden-Adams *et al.*, 2001; Riviere *et al.*, 2002).

Low-level JP-8 exposure can also occur through environmental pathways. JP-8 spills and leaking underground storage tanks contaminate the soil. Of the 1.5 million estimated leaking underground tanks in the U.S. in 1993, 40% are presumed to have leaked to the groundwater (Rodgers *et al.*, 1999). Petroleum fuels are contaminants of concern at an estimated 50 to 60% of all Air Force cleanup sites (Miller, 1994). Weathering of spilled fuel decreases the identifiable mass spectrum peaks to about 200, still a very complex mixture (Rodgers *et al.*, 1999). Even more complex, people environmentally exposed to the weathered fuel may be concurrently exposed to other common groundwater contaminants such as the degreasing solvents, trichloroethylene and perchloroethylene.

Physiologically based pharmacokinetic (PBPK) modeling of mixtures presents a challenge for researchers. A preliminary mixture model for JP-8 in the rat has been proposed that interconnects PBPK models of individual substances via competitive metabolic inhibition, which produces lower overall rates of elimination with increasing chemical complexity (Robinson, 2001). Extrapolation of the rat model to humans is projected for the future. In order to

appropriately test and validate this extrapolation, blood:air and tissue:blood partition coefficients for the individual components are required to describe the relative distribution of each component to the target organ (Gargas, 1991).

The partition coefficient (PC) describes the distribution of a chemical between two media at equilibrium. A tissue:blood PC is necessary for each compartment in the model, to determine the dose distributed by the rate of blood flow to the compartment, which represents a single tissue or lumped (similar) tissues. A blood:air PC is necessary for volatile chemicals to determine uptake from the air to the blood during inhalation and loss of chemical to the air from the blood during exhalation (Gargas, 1991).

PCs can be determined experimentally by several methods. PCs can be measured *in vivo* through steady-state exposure (inhalation or continuous iv injection) followed by rapid analysis of the chemical in each organ. This method works for chemicals that are not metabolized in the body. More frequently, PCs are determined *in vitro*. Vial equilibration is the most common *in vitro* method; a solvent (oil, octanol, saline or water) and blood or tissue (homogenized or unhomogenized) are placed in the bottom of a small vial. The vial is sealed and a known amount of the volatile chemical of interest is injected. The vial is allowed to come to equilibrium; the headspace is sampled and analyzed on a gas chromatograph. This method allows deduction of the concentration in the medium in the bottom of the vial without having to analyze the medium directly (Gargas, 1991; Gargas *et al.*, 1989). Adaptations of this technique exist for nonvolatile chemicals; however, many of these adaptations use expensive custom radiolabeled chemicals to determine the concentration of the chemical at equilibrium between the tissue and the solvent (oil or saline) (Jepson *et al.*, 1994; Murphy *et al.*, 1995). The cost of custom radiolabeled chemicals for *in vitro* experiments and the number of animals needed for *in vivo* PC determination are reasons why nonvolatile PCs are not prevalent in the literature (Poulin and Krishnan, 1995a). Even though volatile PCs are easier to determine, tissue and blood partition coefficients are not available for all, forcing PBPK modelers to look for alternatives (Sweeney *et al.*, 1996). To try to fill this void, several authors have developed algorithms as ways to predict partition coefficients from physical properties.

This project was designed to examine currently available methods for calculating tissue and blood PCs for selected JP-8 mixture components using solvent partition coefficients and to compare the predicted values against published experimental values. In this context, solvents

include water or saline, oil and octanol; the resulting partition coefficients can be found in the literature as water:air, saline:air, oil:air or octanol:water. Additional methods of determining PCs include quantitative structure activity relationships (QSAR) calculations which require extensive databases of physical properties (e.g., three-dimensional structure, octanol:water partition coefficients (calculated or experimentally derived), normal vapor pressure) for hundreds of chemicals and sophisticated computer programs to analyze the relationships between these parameters and the dependent variable (blood:air PC) (Basak, 2002a, 2002b; Gute and Basak, 2001).

METHOD

Literature Searches

Literature searches were performed on the PubMed (free Medline available to public) and Science Citation Index (Thompson ISI, Philadelphia, PA) databases during the period of 23 Jan through 12 Feb 2003. The searches required three major efforts. First solvent PCs were sought using the word "partition", the solvent types (octanol, water, saline, oil) and the chemical names. The chemicals selected for this assessment were those isolated and identified in a published analysis of JP-8 by gas chromatography (McDougal *et al.*, 2000). The 14 most prevalent chemicals in the JP-8 sample were listed along with their concentration (Table 1); isomers (e.g., 1,2,3- vs. 1.2.4-trimethyl benzene) are not distinguishable by this method.

Table 1. Chemical Composition of a JP-8 Sample as Analyzed by Gas Chromatography (McDougal *et al.*, 2000)

Chemical	Concentration (mg/mL)
Undecane	48.4
Dodecane	36.1
Decane	30.2
Tridecane	21.9
Tetradecane	14.6
Methyl naphthalenes	9.9
Trimethyl benzenes	9.7
Nonane	9.2
Pentadecane	8.4
Dimethyl naphthalenes	6.3
Xylenes	4.8
Naphthalene	2.1
Ethyl benzene	1.2
Toluene	0.5

Second, blood:air, tissue:air and tissue:blood PCs were sought using the word "partition", blood or tissue, and the chemical names. Pharmacokinetic models for all the chemicals were also searched, as any PBPK model would require PCs for each chemical. The third literature search effort involved locating articles on calculating PCs. "Partition" was crossed with "predict", "calculate" and "algorithm". Authors found to be prevalent in the field were also researched further (e.g., Krishnan, Basak). Secondary references found within papers were sought for all three literature search efforts.

Experimental PC Tabulation

Solvent PCs were compiled in an Excel spreadsheet. These are tabulated in Appendix A, Table A-1. Water:air and saline:air partition coefficients were combined in the same column. Saline:air has been shown to equal 87 to 97% of the water:air PC for volatile anesthetics. Since this difference is small, introducing little error, and only affects the most volatile compounds, saline:air and water:air PCs can be treated as the same (Meulenberg and Vijverberg, 2000).

Experimental tissue:air, blood:air and tissue:blood values were recorded from published papers and PBPK models. Results were published as either tissue:air or tissue:blood PCs. Since PBPK models require blood:air and tissue:blood PCs, not tissue:air PCs (Gargas, 1991),

experimental tissue:blood PC values were calculated from experimentally derived blood:air and tissue:air PCs by the following equation (Fiserova-Bergerova, 1983; Poulin and Krishnan, 1995a).

$$\frac{Tissue}{Air} / \frac{Blood}{Air} = \frac{Tissue}{Blood} \qquad \text{(Equation 1)}$$

PCs were separated by species (rat and human) and averaged by tissue and chemical. Some data were excluded, as discussed in the Results section. The final values used, after exclusions and averaging, are listed in Tables A-2 and A-3.

PC Calculation

Published algorithms to predict blood and tissue partition coefficients using solvent PCs were recorded in Tables 2 through 5 in the Results section. The characteristics of the equations and the authors' correlation coefficient (R^2) were recorded.

Tissue partition coefficients for selected JP-8 components were calculated in Excel spreadsheets. The number of chemicals for which a PC was calculated for any given algorithm was limited to the availability of the solvent PCs necessary to perform that calculation; if a specific solvent PC was not available for a chemical then any equation using that solvent PC could not be worked to completion.

Some authors' algorithms directly calculate tissue:blood PCs (direct equations) while the majority result in tissue:air values. Equation 1 was used to predict the tissue:blood PC from a calculated tissue:air PC value. For each predicted tissue:air value, tissue:blood calculations were performed twice. First, an experimentally derived blood:air value was used in the denominator of Equation 1, resulting in a PC_{EB} value. Second, a predicted blood:air value, using the appropriate algorithm from the same author, was used to determine a tissue:blood PC_{PB}.

Algorithm results generated in Excel were then evaluated in SAS (Statistical Analysis System, SAS Institute, Inc., Cary, NC). The figures in this report were prepared in SAS. The adequacy of predictive algorithms was evaluated on three levels. First, the performance of solvent based

algorithms as a whole was evaluated, ranked by absolute percent error. Twenty percent of the measured value was used as a metric for overall comparison. Normal biological variation in blood:air partition coefficients has been observed at 20% (Gearhart *et al.*, 1993). Second, each algorithm's average performance by organ was compared against experimental levels using percent error plots and absolute percent error. The consistency of prediction was noted (e.g., always over- or under-predicts compared to experimental values) and the adequacy of prediction of alkane PCs (when available) was considered. Although the majority of JP-8 (Table 1) consists of straight chain hydrocarbons, the most data are available for the aromatic constituents. Third, absolute percent error was used to compare each PC_{EB} and PC_{PB} set to determine which results in tissue:blood values closer to experimental PCs. The minimum, median and maximum relative differences between PC_{EB} and PC_{PB} values were found using Equation 2.

$$\textit{Relative Difference} = \frac{100 \times \left| PC_{EB} - PC_{PB} \right|}{\dfrac{PC_{EB} + PC_{PB}}{2}} \qquad \text{(Equation 2)}$$

The percentage of occurrences where the PC_{EB} value had a smaller absolute percent error than the PC_{PB} value was calculated.

RESULTS

Literature Search Results

One or more solvent PCs were found for all JP-8 components sought. Octanol:water PCs were found for all compounds in Table 1; handbooks of physical chemistry often list this parameter (Yaws *et al.*, 1999). Octanol:water PCs are most often measured at 25°C. Some literature sources did not state the temperature at which this parameter was measured, but the values were similar to or the same as values measured at 25°C from different sources. Therefore, when more than one octanol:water PC existed for a chemical, the values were averaged. One resource measured octanol:water PC at 37°C (Poulin and Krishnan, 1995b); this value was excluded as all others were at 25°C and there was a 25°C value available for that compound (toluene). Temperature purportedly does not affect octanol:water partitioning greatly (Leo,

personal communication, 2003). The toluene log octanol:water PCs were 2.65 and 2.73 at 37 and 25°C, respectively (Gute and Basak, 2001; Poulin and Krishnan, 1995b; Yaws *et al.*, 1999).

The other solvent PCs (water or saline:air, vegetable or olive oil:air) were harder to find. This challenging situation has been noted in the literature (Poulin and Krishnan, 1995b). These values were measured at 37°C in all cases.

Empirical tissue and blood PCs were available for several of the more common aromatics (toluene, ethyl benzene, xylenes) and only two aliphatics (decane and nonane). The best sources for these parameters were papers describing methods for experimental partition coefficient determination (e.g., Gargas *et al.*, 1988, 1989; Kumarathasan *et al.*, 1998).

Experimental PC Values

When multiple tissue and blood PC values were found for a chemical in a tissue, only values from primary, experimentally derived sources were used in the average. All primary resources used vial equilibration for PC determination (Gargas *et al.*, 1989; Kaneko *et al.*, 2000a; Kumarathasan *et al.*, 1998; Pierce *et al.*, 1996; Robinson, 2000). Secondary sources did not state how PCs were determined (Fiserova-Bergerova, 1983; Kaneko *et al.*, 2000b) and are always subject to compounded translation errors.

Other values that were excluded from the averages reported in Table A-2 include those from older rats. Kumarathasan *et al.* (1998) used mature (350 g) male Sprague-Dawley rats in several of their experiments, contrasting their results with those of 250 g young adult males of the same strain. PC values were found to be lower in the younger rats and more comparable to those published by Gargas *et al.* (1989), who used 200 to 300 g Fischer 344 male rats (Kumarathasan *et al.*, 1998). It is expected that these values from younger rats would be more useful in a PBPK model as young adult specimens typically are used in kinetic studies for validation. Age increased PCs in blood, brain, fat, kidneys, liver and muscle by an average of 49, 160, 64, 240, 190 and 130%, respectively, for m- and p-xylene. The authors projected that the higher PC values could be due to higher fat concentrations or altered fat composition in the older animal tissues (Kumarathasan *et al.*, 1998). Partition coefficients have been found to vary with changes in hematocrit, blood lipids (fasted versus postprandial sampling) and organ lipids (Fiserova-Bergerova, 1983).

Kumarathasan *et al.* (1998) reported tissue:blood PCs instead of tissue:air for their experiments with 250 g rats. For m- and p-xylene, the authors provided a blood:air PC, allowing back-calculation to determine tissue:air PCs compatible for comparison with values from other studies (reverse of Equation 1). There were no blood:air PCs listed for ethyl benzene and o-xylene. Young adult rat blood:air PCs were calculated instead from mature rat PCs reduced by 49%, the average percent difference calculated between mature and young adult blood PCs for m- and p-xylene. For o-xylene, this calculation resulted in a reduction of the blood:air PC from 61.6 to 41.4, a similar value to 44.3, reported in Gargas *et al.* (1989). A comparable value for ethyl benzene was not found but the calculation reduced the PC from 64.6 to 43.4 and allowed more credible back-calculations for the tissue:air PCs.

Fiserova-Bergerova (1983) reported PCs for toluene in several rat tissues (Table A-2), which are consistently lower than experimentally derived values from other sources (64, 30, 62 and 35% lower than experimental values for blood, fat, kidney, liver and muscle, respectively). Because experimental details were not available, the secondary values were excluded from averages of toluene PCs for these tissues. Fiserova-Bergerova's secondary values for additional tissues not found in other studies (brain, heart, kidney and lung) remain in Table A-2.

Human PCs were also collected and listed in Table A-3, since the ultimate goal is to predict the outcomes of exposure to mixtures in the population of concern, deployed military personnel (Robinson, 2001). Sources of human PCs included secondary literature references (Fiserova-Bergerova, 1983; Tardif *et al.*, 1995) and vial equilibration experiments using blood from volunteers or fat samples from patients undergoing surgery (Gargas *et al.*, 1989; Jarnberg and Johanson, 1995; Pierce *et al.*, 1996).

Where more than one value for a chemical and tissue was available, only results from similar experiments and techniques were averaged. For this reason, experiments made with perdeuterated compounds were excluded but parallel nondeuterated PCs were used in the average. Although comparison of the perdeuterated chemical PCs with the nondeuterated PCs revealed that they were not statistically different for all chemicals tested (ethyl benzene, toluene, m- and o-xylene) except for one (p-xylene) (Pierce *et al.*, 1996), none of the other chemicals for which PCs were found were radiolabeled, making the non-radiolabeled numbers more comparable.

A fasted value for toluene was excluded in the average blood:air PC in humans. During fasting, blood lipids decrease, resulting in a lower blood:air PC (Fiserova-Bergerova, 1983). Since the other studies did not specify the food status of subjects, it is assumed that blood was taken in various fasted or postprandial states depending on the individual. The one to two hour postprandial value (Fiserova-Bergerova, 1983) was comparable to values from different sources and was kept in the final average for this chemical.

Back calculations to derive tissue:air PCs were performed using the reverse of Equation 1. Tissue:blood PC values were multiplied by the blood:air PC value reported by the same authors in the same study (e.g., Kumarathasan *et al.* (1998) fat:air value for 250 g rats was divided by the blood:air value for 250 g rats). However, blood:air PCs were not always reported in each study. For example, Fiserova-Bergerova (1983) did not report a blood:air PC for toluene in rats, so the tissue:blood values were multiplied by the experimental blood:air value reported by Gargas *et al.* (1989). Calculations to determine tissue:blood PCs from tissue:air and blood:air PCs were completed using Equation 1 with values from the same study whenever possible. These calculated values are listed in Tables A-2 and A-3.

Calculated PC Results

Several solvent PC based equations were found to predict tissue and blood PCs. These equations are listed in Tables 2 through 5. The equations were categorized as rat or human and according to the result of the equation (tissue:air or blood:air versus tissue:blood). Three types of equations were found. Empirical equations are derived from linear regressions with experimental data. These equations are assumed to provide best estimated values for chemicals similar to the type of compounds used to derive the equation. For example, low molecular weight volatile PCs are expected to be predicted better by Equation 5 than Equation 6 (see Table 2) as PCs from this type of compound were used by Gargas *et al.* (1989) to develop Equation 5 (Payne and Kenny, 2002). The authors' R^2 values were included in the table, when available, to show the strength of relationship between the experimental data used to derive the equation and the equation predicted values.

Physiologically based equations take into account the water and lipid make-up of the tissue in question. Poulin and Krishnan (1996a) (e.g., Table 2, Equation 3) describe blood and other

tissues as being made up of tissue water, neutral lipids (non-polar lipids including triglycerides and cholesterol) and phospholipids (lipids with a phosphoric acid ester on the glycerol molecule including phosphatidyl choline). Phospholipids are both lipid and water soluble. Physiologically based equations do not contain any additional empirical components and are not fitted through regression.

Hybrid equations combine elements of physiologically based and empirical equations (e.g., Table 2, Equation 4). The authors of hybrid equations attempt to account for lipophilic and hydrophilic components of each tissue, and then add an empirical component to adjust for systematic errors in the fit of the equation or to represent protein binding in the blood or tissue (Meulenberg and Vijverberg, 2000). Like strict empirical equations, the predicted PCs from hybrid equations are expected to be more accurate, for example, for volatiles if they were derived from volatiles and, therefore, are not expected to work as well for non-volatiles (DeJongh *et al.*, 1997). The authors' R^2 values were included in the table, when available.

Table 2 Rat Blood:Air and Tissue:Air Algorithms

Eq.	Algorithm	Authors' R^2	Characteristics	Source
	Blood:Air			
3	$P_{b:a} = P_{o:w}P_{w:a}(a+0.3b)+P_{w:a}(c+0.7b)$ $P_{b:a} = P_{o:w}P_{w:a}(0.0013+0.00060)+P_{w:a}(0.84+0.0014)$	NA	* a, b and c are the fractions of neutral lipids, phospholipids and water in tissue, respectively	Poulin and Krishnan, 1996a
4	$P_{b:a} = aP_{oil:a} + bP_{s:a} + c$ $P_{b:a} = 0.0054P_{oil:a} + 0.931P_{s:a} + 1.16$	0.93	* a and b represent lipophilic and hydrophilic portions of tissue, respectively * c is an empirical coefficient intended to compensate for systematic errors in solvent PCs	Meulenberg and Vijverberg, 2000
5	$\log P_{b:a} = 0.553(\log P_{oil:a}) + 0.351(\log P_{s:a}) - 0.286$	0.928	* an empirical relationship based on linear regression using experimental data on low molecular weight volatiles	Gargas *et al.*, 1989
6	$\log P_{b:a} = 0.426(\log P_{oil:a}) + 0.515(\log P_{s:a}) - 0.070$	0.9536	* an empirical relationship based on linear regression using experimental data on halogenated alkanes	Gargas *et al.*, 1988
	Brain:Air			
7	$P_{t:a} = aP_{oil:a} + bP_{s:a} + c$ $P_{t:a} = 0.054P_{oil:a} + 0.832P_{s:a} + 0$	0.90	* a and b represent lipophilic and hydrophilic portions of tissue, respectively * c is an empirical coefficient intended to compensate for systematic errors in solvent PCs	Meulenberg and Vijverberg, 2000

Eq.	Algorithm	Authors' R^2	Characteristics	Source
	Fat:Air			
8	$P_{t:a} = P_{o:w}P_{w:a}(a+0.3b) + P_{w:a}(c+0.7b)$ $P_{t:a} = P_{o:w}P_{w:a}(0.853+0.0006) + P_{w:a}(0.12+0.0014)$	NA	* a, b and c are the fractions of neutral lipids, phospholipids and water in tissue, respectively	Poulin and Krishnan, 1996a
9	$P_{t:a} = aP_{oil:a} + bP_{s:a} + c$ $P_{t:a} = 0.594P_{oil:a} + 0.085P_{s:a} + 9.40$	0.86	* a and b represent lipophilic and hydrophilic portions of tissue, respectively * c is an empirical coefficient intended to compensate for systematic errors in solvent PCs	Meulenberg and Vijverberg, 2000
10	$\log P_{t:a} = 0.927(\log P_{oil:a}) - 0.032(\log P_{s:a}) + 0.120$	0.947	* an empirical relationship based on linear regression using experimental data on low molecular weight volatiles	Gargas *et al.*, 1989
11	$\log P_{t:a} = 1.027(\log P_{oil:a}) - 0.046(\log P_{s:a}) - 0.119$	0.9701	* an empirical relationship based on linear regression using experimental data on halogenated alkanes	Gargas *et al.*, 1988
	Kidney:Air			
12	$P_{t:a} = aP_{oil:a} + bP_{s:a} + c$ $P_{t:a} = 0.097P_{oil:a} + 0.826P_{s:a} + 0$	0.91	* a and b represent lipophilic and hydrophilic portions of tissue, respectively * c is an empirical coefficient intended to compensate for systematic errors in solvent PCs; c was not determined for this tissue	Meulenberg and Vijverberg, 2000
	Liver:Air			
13	$P_{t:a} = P_{o:w}P_{w:a}(a+0.3b) + P_{w:a}(c+0.7b)$ $P_{t:a} = P_{o:w}P_{w:a}(0.035+0.0075) + P_{w:a}(0.70+0.0175)$	NA	* a, b and c are the fractions of neutral lipids, phospholipids and water in tissue, respectively	Poulin and Krishnan, 1996a
14	$P_{t:a} = aP_{oil:a} + bP_{s:a} + c$ $P_{t:a} = 0.026P_{oil:a} + 0.878P_{s:a} + 2.36$	0.92	* a and b represent lipophilic and hydrophilic portions of tissue, respectively * c is an empirical coefficient intended to compensate for systematic errors in solvent PCs	Meulenberg and Vijverberg, 2000
15	$\log P_{t:a} = 0.730(\log P_{oil:a}) + 0.128(\log P_{s:a}) - 0.550$	0.903	* an empirical relationship based on linear regression using experimental data on low molecular weight volatiles	Gargas *et al.*, 1989
16	$\log P_{t:a} = 0.574(\log P_{oil:a}) + 0.302(\log P_{s:a}) - 0.278$	0.9450	* an empirical relationship based on linear regression using experimental data on halogenated alkanes	Gargas *et al.*, 1988

Eq.	Algorithm	Authors' R^2	Characteristics	Source
	Muscle:Air			
17	$P_{t:a} = P_{o:w}P_{w:a}(a+0.3b)+P_{w:a}(c+0.7b)$ $P_{t:a} = P_{o:w}P_{w:a}(0.009+0.003)+P_{w:a}(0.74+0.007)$	NA	* a, b and c are the fractions of neutral lipids, phospholipids and water in tissue, respectively	Poulin and Krishnan, 1996a
18	$P_{t:a} = aP_{oil:a} + bP_{s:a} + c$ $P_{t:a} = 0.010P_{oil:a} + 0.772P_{s:a} + 0.29$	0.82	* a and b represent lipophilic and hydrophilic portions of tissue, respectively * c is an empirical coefficient intended to compensate for systematic errors in solvent PCs	Meulenberg and Vijverberg, 2000
19	$\log P_{t:a} = 0.644(\log P_{oil:a}) + 0.180(\log P_{s:a}) - 0.725$	0.879	* an empirical relationship based on linear regression using experimental data on low molecular weight volatiles	Gargas *et al.*, 1989
20	$\log P_{t:a} = 0.477(\log P_{oil:a}) + 0.365(\log P_{s:a}) - 0.374$	0.9382	* an empirical relationship based on linear regression using experimental data on halogenated alkanes	Gargas *et al.*, 1988

Note: Coefficients a-c are defined in each row; NA = not applicable (to physiological equations);
Subscripts are: a = air, b = blood, s = saline, t = tissue, w = water

Table 3 Human Blood:Air and Tissue:Air Algorithms

Eq.	Algorithm	Authors' R^2	Characteristics	Source
	Blood:Air			
21	$P_{b:a} = P_{o:w}P_{w:a}(a+0.3b)+P_{w:a}(c+0.7b)$ $P_{b:a} = P_{o:w}P_{w:a}(0.0033+0.00072)+P_{w:a}(0.82+0.0017)$	NA	* a, b and c are the fractions of neutral lipids, phospholipids and water in tissue, respectively	Poulin and Krishnan, 1996a
22	$P_{b:a} = aP_{oil:a} + bP_{s:a} + c$ $P_{b:a} = 0.0072P_{oil:a} + 0.898P_{s:a} + 0.03$	0.99	* a and b represent lipophilic and hydrophilic portions of tissue, respectively * c is an empirical coefficient intended to compensate for systematic errors in solvent PCs	Meulenberg and Vijverberg, 2000
23	$\log P_{b:a} = 0.581(\log P_{oil:a}) + 0.332(\log P_{s:a}) - 0.599$	0.875	* an empirical relationship based on linear regression using experimental data on low molecular weight volatiles	Gargas *et al.*, 1989
24	$\log P_{b:a} = 0.180(\log P_{oil:a}) + 0.889(\log P_{w:a}) + 0.054$	not reported	* an empirical relationship based on linear regression from a previous publication	Tichy, 1991
25	$\log P_{b:a} = (-0.102) + 0.675(\log P_{w:a}) + 0.315(\log P_{oil:a})$	0.9951	* an empirical relationship based on double regression using literature solvent and tissue PC values	Abraham *et al.*, 1985
	Brain:Air			
26	$P_{t:a} = aP_{oil:a} + bP_{s:a} + c$ $P_{t:a} = 0.020P_{oil:a} + 0.380P_{s:a} + 0.94$	0.98	* a and b represent lipophilic and hydrophilic portions of tissue, respectively * c is an empirical coefficient intended to compensate for systematic errors in solvent PCs	Meulenberg and Vijverberg, 2000
27	$\log P_{t:a} = 0.471(\log P_{oil:a}) + 0.630(\log P_{w:a}) - 0.305$	not reported	* an empirical relationship based on linear regression from a previous publication	Tichy, 1991
28	$\log P_{t:a} = (-0.274) + 0.537(\log P_{w:a}) + 0.444(\log P_{oil:a})$	0.9945	* an empirical relationship based on double regression using literature solvent and tissue PC values	Abraham *et al.*, 1985

Eq.	Algorithm	Authors' R^2	Characteristics	Source
	Fat:Air			
29	$P_{t:a} = P_{o:w}P_{w:a}(a+0.3b)+P_{w:a}(c+0.7b)$ $P_{t:a} = P_{o:w}P_{w:a}(0.798+0.0006)+P_{w:a}(0.15+0.0014)$	NA	* a, b and c are the fractions of neutral lipids, phospholipids and water in tissue, respectively	Poulin and Krishnan, 1996a
30	$P_{t:a} = aP_{oil:a}+bP_{s:a}+c$ $P_{t:a} = 0.447P_{oil:a}+0.075P_{s:a}+6.59$	0.92	* a and b represent lipophilic and hydrophilic portions of tissue, respectively * c is an empirical coefficient intended to compensate for systematic errors in solvent PCs	Meulenberg and Vijverberg, 2000
31	$\log P_{t:a} = 0.782(\log P_{oil:a})+0.201(\log P_{w:a})+0.432$	not reported	* an empirical relationship based on linear regression from a previous publication	Tichy, 1991
32	$\log P_{t:a} = (0.209)+0.0628(\log P_{w:a})+0.8868(\log P_{oil:a})$	0.9988	* an empirical relationship based on double regression using literature solvent and tissue PC values	Abraham *et al.*, 1985
	Kidney:Air			
33	$P_{t:a} = aP_{oil:a}+bP_{s:a}+c$ $P_{t:a} = 0.011P_{oil:a}+0.400P_{s:a}+0.69$	0.98	* a and b represent lipophilic and hydrophilic portions of tissue, respectively * c is an empirical coefficient intended to compensate for systematic errors in solvent PCs	Meulenberg and Vijverberg, 2000
34	$\log P_{t:a} = 0.466(\log P_{oil:a})+0.379(\log P_{w:a})-0.332$	not reported	* an empirical relationship based on linear regression from a previous publication	Tichy, 1991
35	$\log P_{t:a} = (-0.391)+0.550(\log P_{w:a})+0.440(\log P_{oil:a})$	0.9958	* an empirical relationship based on double regression using literature solvent and tissue PC values	Abraham *et al.*, 1985
	Liver:Air			
36	$P_{t:a} = P_{o:w}P_{w:a}(a+0.3b)+P_{w:a}(c+0.7b)$ $P_{t:a} = P_{o:w}P_{w:a}(0.039+0.0084)+P_{w:a}(0.72+0.020)$	NA	* a, b and c are the fractions of neutral lipids, phospholipids and water in tissue, respectively	Poulin and Krishnan, 1996a
37	$P_{t:a} = aP_{oil:a}+bP_{s:a}+c$		* a represents lipophilic portions of tissue *** b was not determined for human liver** * c is an empirical coefficient intended to compensate for systematic errors in solvent PCs	Meulenberg and Vijverberg, 2000
38	$\log P_{t:a} = 0.746(\log P_{oil:a})+0.178(\log P_{w:a})-0.767$	not reported	* an empirical relationship based on linear regression from a previous publication	Tichy, 1991
39	$\log P_{t:a} = (-0.388)+0.502(\log P_{w:a})+0.497(\log P_{oil:a})$	0.9970	* an empirical relationship based on double regression using literature solvent and tissue PC values	Abraham *et al.*, 1985

Eq.	Algorithm	Authors' R^2	Characteristics	Source
	Lung:Air			
40	$\log P_{t:a} = 0.373(\log P_{oil:a}) + 0.416(\log P_{w:a}) - 0.216$	not reported	* an empirical relationship based on linear regression from a previous publication	Tichy, 1991
41	$\log P_{t:a} = (-0.057) + 0.870(\log P_{w:a}) + 0.146(\log P_{oil:a})$	0.9993	* an empirical relationship based on double regression using literature solvent and tissue PC values	Abraham *et al.*, 1985
	Muscle:Air			
42	$P_{t:a} = P_{o:w}P_{w:a}(a + 0.3b) + P_{w:a}(c + 0.7b)$ $P_{t:a} = P_{o:w}P_{w:a}(0.035 + 0.003) + P_{w:a}(0.75 + 0.007)$	NA	* a, b and c are the fractions of neutral lipids, phospholipids and water in tissue, respectively	Poulin and Krishnan, 1996a
43	$P_{t:a} = aP_{oil:a} + bP_{s:a} + c$ $P_{t:a} = 0.014P_{oil:a} + 0.384P_{s:a} + 0.94$		* a represents lipophilic portions of tissue * **b was not determined for human liver** * c is an empirical coefficient intended to compensate for systematic errors in solvent PCs	Meulenberg and Vijverberg, 2000
44	$\log P_{t:a} = (-0.263) + 0.575(\log P_{w:a}) + 0.423(\log P_{oil:a})$	0.9877	* an empirical relationship based on double regression using literature solvent and tissue PC values	Abraham *et al.*, 1985

Note: Coefficients a-c are defined in each row; NA = not applicable (to physiological equations);
Subscripts are: a = air, b = blood, o = octanol, s = saline, t = tissue, w = water

Table 4 Rat Tissue:Blood (Direct) Algorithms

Eq.	Algorithm	Authors' R^2	Characteristics	Source
	Fat:Blood			
45	$P_{t:b} = \frac{aK_{o:w}^{c} + b}{dK_{o:w}^{c} + e} + f$ $P_{t:b} = \frac{0.8K_{o:w}^{0.70} + 0.2}{0.004K_{o:w}^{0.70} + 0.996} + (-0.02)$	0.98	* a and b are fat and water fractions by weight of the tissue, respectively * c describes the correlation between the partitioning processes in two different media * d and e are fat and water fractions by weight of the blood, respectively * f is an empirical correction to account for partitioning not described by the equation (e.g., protein binding)	DeJongh *et al.*, 1997
46	$P_{t:b} = \frac{P_t}{(0.37P_e) + (0.63P_p)}$ $P_t = aK_{o:w} + b + 0.3cK_{o:w} + 0.7c$ $P_e = dK_{o:w} + f + 0.3gK_{o:w} + 0.7g$ $P_p = hK_{o:w} + i + 0.3jK_{o:w} + 0.7j$ $P_t = 0.9975K_{o:w} + 0.12 + 0.00075K_{o:w} + 0.0018$ $P_e = 0.23K_{o:w} + 0.63 + 0.23K_{o:w} + 0.54$ $P_p = 0.639K_{o:w} + 0.96 + 0.108K_{o:w} + 0.253$	NA	* based on composition of tissue and blood (37% erythrocytes, 63% plasma) *a, d and h are fractions of neutral lipids in the respective tissues * b, f and i are fractions of water in the tissues * c, g and j are fractions of phospholipids in the tissues	Poulin and Krishnan, 1995b

Eq.	Algorithm	Authors' R^2	Characteristics	Source
	Liver:Blood			
47	$P_{t:b} = \frac{aK_{o:w}^{c} + b}{dK_{o:w}^{c} + e} + f$ $P_{t:b} = \frac{0.081K_{o:w}^{0.44} + 0.919}{0.004K_{o:w}^{0.44} + 0.996} + (-0.19)$	0.58	* a and b are fat and water fractions by weight of the tissue, respectively * c describes the correlation between the partitioning processes in two different media * d and e are fat and water fractions by weight of the blood, respectively * f is an empirical correction to account for partitioning not described by the equation (e.g., protein binding)	DeJongh *et al.*, 1997
48	$P_{t:b} = \frac{P_t}{(0.37P_e) + (0.63P_p)}$ $P_t = aK_{o:w} + b + 0.3cK_{o:w} + 0.7c$ $P_e = dK_{o:w} + f + 0.3gK_{o:w} + 0.7g$ $P_p = hK_{o:w} + i + 0.3jK_{o:w} + 0.7j$ $P_t = 0.58K_{o:w} + 0.70 + 0.126K_{o:w} + 0.294$ $P_e = 0.23K_{o:w} + 0.63 + 0.23K_{o:w} + 0.54$ $P_p = 0.639K_{o:w} + 0.96 + 0.108K_{o:w} + 0.253$	NA	* based on composition of tissue and blood (37% erythrocytes, 63% plasma) *a, d and h are fractions of neutral lipids in the respective tissues * b, f and i are fractions of water in the tissues * c, g and j are fractions of phospholipids in the tissues	Poulin and Krishnan, 1995b

Eq.	Algorithm	Authors' R^2	Characteristics	Source
	Muscle:Blood			
49	$P_{t:b}=\frac{aK_{o:w}^{c}+b}{dK_{o:w}^{c}+e}+f$ $P_{t:b}=\frac{0.056K_{o:w}^{0.29}+0.944}{0.004K_{o:w}^{0.29}+0.996}+(-0.55)$	0.24	* a and b are fat and water fractions by weight of the tissue, respectively * c describes the correlation between the partitioning processes in two different media * d and e are fat and water fractions by weight of the blood, respectively * f is an empirical correction to account for partitioning not described by the equation (e.g., protein binding)	DeJongh *et al.*, 1997
50	$P_{t:b}=\frac{P_t}{(0.37P_e)+(0.63P_p)}$ $P_t=aK_{o:w}+b+0.3cK_{o:w}+0.7c$ $P_e=dK_{o:w}+f+0.3gK_{o:w}+0.7g$ $P_p=hK_{o:w}+i+0.3jK_{o:w}+0.7j$ $P_t=0.459K_{o:w}+0.743+0.162K_{o:w}+0.379$ $P_e=0.23K_{o:w}+0.63+0.23K_{o:w}+0.54$ $P_p=0.639K_{o:w}+0.96+0.108K_{o:w}+0.253$	NA	* based on composition of tissue and blood (37% erythrocytes, 63% plasma) *a, d and h are fractions of neutral lipids in the respective tissues * b, f and i are fractions of water in the tissues * c, g and j are fractions of phospholipids in the tissues	Poulin and Krishnan, 1995b

Note: Coefficients a-j are defined in each row; NA = not applicable (to physiological equations);
Subscripts are: b = blood, e = erythrocytes, o = octanol, p = plasma, t = tissue, w = water

Table 5 Human Tissue:Blood (Direct) Algorithms

Eq.	Algorithm	Authors' R^2	Characteristics	Source
	Brain:Blood			
50	$P_{t:b} = \frac{aK_{o:w}^{c} + b}{dK_{o:w}^{c} + e} + f$ $P_{t:b} = \frac{0.146K_{o:w}^{0.48} + 0.854}{0.007K_{o:w}^{0.48} + 0.993} + (-0.21)$	1.00	* a and b are fat and water fractions by weight of the tissue, respectively * c describes the correlation between the partitioning processes in two different media * d and e are fat and water fractions by weight of the blood, respectively * f is an empirical correction to account for partitioning not described by the equation (e.g., protein binding)	DeJongh *et al.*, 1997
51	$\log P_{t:b} = \log\frac{(0.08099 - 0.02742) \times K_{o:w}^{0.737} + 1}{0.004130 \times K_{o:w}^{0.737} + 1} - 0.205$	0.978	* hybrid equation combining protein, lipid and water fractions of a tissue, representing membrane accumulation and protein binding, with nonlinear regression optimization	Balaz and Lukacova, 1999
52	$P_{t:b} = 0.0372P_{f:b} + 0.5199$	0.9693	*requires $P_{fat:blood}$ *empirical relationship based on regression using experimental data on alcohols partitioning	Fiserova-Bergerova and Diaz, 1986
	Fat:Blood			
53	$P_{t:b} = \frac{aK_{o:w}^{c} + b}{dK_{o:w}^{c} + e} + f$ $P_{t:b} = \frac{0.8K_{o:w}^{1.03} + 0.2}{0.007K_{o:w}^{1.03} + 0.993} + (-0.38)$	1.00	* a and b are fat and water fractions by weight of the tissue, respectively * c describes the correlation between the partitioning processes in two different media * d and e are fat and water fractions by weight of the blood, respectively * f is an empirical correction to account for partitioning not described by the equation (e.g., protein binding)	DeJongh *et al.*, 1997
54	$\log P_{t:b} = \log\frac{(7.274 - 6.075) \times K_{o:w}^{0.926} + 1}{0.003960 \times K_{o:w}^{0.926} + 1} - 0.982$	0.980	* hybrid equation combining protein, lipid and water fractions of a tissue, representing membrane accumulation and protein binding, with nonlinear regression optimization	Balaz and Lukacova, 1999

Eq.	Algorithm	Authors' R^2	Characteristics	Source
	Heart:Blood			
55	$\log P_{t:b} = 0.245 \times \log K_{o:w} + \log(1+0) - \log(K_{o:w}^{0.245} \times 0.1971 + 1) + 0$	0.965	* hybrid equation combining protein, lipid and water fractions of a tissue, representing membrane accumulation and protein binding, with nonlinear regression optimization	Balaz and Lukacova, 1999
	Kidney:Blood			
56	$P_{t:b} = \frac{aK_{o:w}^{c} + b}{dK_{o:w}^{c} + e} + f$ $P_{t:b} = \frac{0.06K_{o:w}^{0.57} + 0.94}{0.007K_{o:w}^{0.57} + 0.993} + (-0.19)$	1.00	* a and b are fat and water fractions by weight of the tissue, respectively * c describes the correlation between the partitioning processes in two different media * d and e are fat and water fractions by weight of the blood, respectively * f is an empirical correction to account for partitioning not described by the equation (e.g., protein binding)	DeJongh *et al.*, 1997
56	$\log P_{t:b} = \log \frac{(0.04647 - 0.02369) \times K_{o:w}^{0.686} + 1}{0.003490 \times K_{o:w}^{0.686} + 1} - 0.154$	0.961	* hybrid equation combining protein, lipid and water fractions of a tissue, representing membrane accumulation and protein binding, with nonlinear regression optimization	Balaz and Lukacova, 1999
57	$P_{t:b} = 0.0211 P_{f:b} + 0.6442$	0.9719	*requires $P_{fat:blood}$ *empirical relationship based on regression using experimental data on alcohols partitioning	Fiserova-Bergerova and Diaz, 1986

Eq.	Algorithm	Authors' R^2	Characteristics	Source
	Liver:Blood			
58	$P_{t:b} = \frac{aK_{o:w}^{c} + b}{dK_{o:w}^{c} + e} + f$ $P_{t:b} = \frac{0.065K_{o:w}^{0.81} + 0.935}{0.007K_{o:w}^{0.81} + 0.993} + (-0.35)$	0.99	* a and b are fat and water fractions by weight of the tissue, respectively * c describes the correlation between the partitioning processes in two different media * d and e are fat and water fractions by weight of the blood, respectively * f is an empirical correction to account for partitioning not described by the equation (e.g., protein binding)	DeJongh *et al.*, 1997
59	$\log P_{t:b} = 0.548 \times \log K_{o:w} + \log(1-0.4340)$ $-\log(K_{o:w}^{0.548} \times 0.01412 + 1) - 0.645$	0.965	* hybrid equation combining protein, lipid and water fractions of a tissue, representing membrane accumulation and protein binding, with nonlinear regression optimization	Balaz and Lukacova, 1999
60	$P_{t:b} = 0.0425P_{f:b} + 0.5770$	0.9586	*requires $P_{fat:blood}$ *empirical relationship based on regression using experimental data on alcohols partitioning	Fiserova-Bergerova and Diaz, 1986
	Lung:Blood			
61	$\log P_{t:b} = 0.167 \times \log K_{o:w} + \log(1-0.4054)$ $-\log(K_{o:w}^{0.167} \times 0.2408 + 1) + 0$	0.842	* hybrid equation combining protein, lipid and water fractions of a tissue, representing membrane accumulation and protein binding, with nonlinear regression optimization	Balaz and Lukacova, 1999
62	$P_{t:b} = 0.00461P_{f:b} + 1.0701$	0.7357	*requires $P_{fat:blood}$ *empirical relationship based on regression using experimental data on alcohols partitioning	Fiserova-Bergerova and Diaz, 1986

Eq.	Algorithm	Authors' R^2	Characteristics	Source
	Muscle:Blood			
63	$P_{t:b} = \frac{aK_{o:w}^{c} + b}{dK_{o:w}^{c} + e} + f$ $P_{t:b} = \frac{0.04K_{o:w}^{0.81} + 0.96}{0.007K_{o:w}^{0.81} + 0.993} + (-0.22)$	1.00	* a and b are fat and water fractions by weight of the tissue, respectively * c describes the correlation between the partitioning processes in two different media * d and e are fat and water fractions by weight of the blood, respectively * f is an empirical correction to account for partitioning not described by the equation (e.g., protein binding)	DeJongh *et al.*, 1997
64	$\log P_{t:b} = \log \frac{(0.1107 - 0.04922) \times K_{o:w}^{0.637} + 1}{0.006210 \times K_{o:w}^{0.637} + 1} - 0.198$	0.953	* hybrid equation combining protein, lipid and water fractions of a tissue, representing membrane accumulation and protein binding, with nonlinear regression optimization	Balaz and Lukacova, 1999
65	$P_{t:b} = 0.0326P_{f:b} + 0.4504$	0.9632	*requires $P_{fat:blood}$ *empirical relationship based on regression using experimental data on alcohols partitioning	Fiserova-Bergerova and Diaz, 1986

Note: Coefficients a-f are defined in each row; Subscripts are: b = blood, f = fat, o = octanol, t = tissue, w = water

As there were few sources for solvent PC based equations for direct human tissue:blood PCs (Table 5), fat:blood PC based equations by Fiserova-Bergerova and Diaz (1986) were included (e.g., Table 5, Equation 44). The small number of chemicals with experimental fat:blood PCs in humans limited the number of predicted PCs calculable for this set of equations.

Overall Performance of Algorithms

Complete results for all algorithms, tissues and chemicals are listed in Appendix B. The percent errors for each blood:air and PC_{EB} tissue:blood calculation for rats and humans are listed below in Tables 6 and 7, respectively.

Table 6: Percent Error from Rat Blood:Air and Tissue:Blood (Direct and PC_{EB} Equations) Algorithms

		Percent Error					
Tissue	Chemical	D	G8	G9	M	P5	P6
Blood:Air	Decane		-83	-13	356		-95
	Ethyl benzene		-16	34	-48		-87
	Toluene		31	72	-52		-79
	Xylene, m-		-8	43	-46		-83
	Xylene, o-		8	60	-44		-80
	Xylene, p-		-8	44	-45		-85
Brain:Blood	Ethyl benzene				480		
	Toluene				-23		
	Xylene, m-				294		
	Xylene, o-				186		
	Xylene, p-				306		
Fat:Blood	Ethyl benzene	118	120	68	41	-96	28
	Nonane	-28				-99	
	Toluene	-10	-5	-17	-36	-97	-8
	Xylene, m-	71	66	28	8	-97	23
	Xylene, o-	34	42	9	-7	-97	18
	Xylene, p-	70	80	39	16	-97	11
Kidney:Blood	Toluene				234		
Liver:Blood	Ethyl benzene	104	32	132	93	-8	93
	Nonane	415				-15	
	Toluene	-59	-58	-41	-62	-76	-44
	Xylene, m-	37	-9	58	28	-40	63
	Xylene, o-	2	-22	28	2	-54	43
	Xylene, p-	26	-12	54	25	-43	34
Muscle:Blood	Ethyl benzene	-19	-41	-6	-11	-3	-33
	Nonane	5				-30	
	Toluene	-54	-45	-32	-55	-37	-48
	Xylene, m-	-14	-34	3	-5	1	-9
	Xylene, o-	-30	-39	-9	-19	-16	-15
	Xylene, p-	-24	-40	-5	-11	-8	-29

Notes: D = DeJongh *et al.* (1997) (H), G8 = Gargas *et al.* (1988) (E), G9 = Gargas *et al.* (1989) (E), M = Meulenberg and Vijverberg (2000) (H), P5 = Poulin and Krishnan (1995b) (P), P6 = Poulin and Krishnan (1996a) (P), where (E) = empirical, (H) = hybrid and (P) = physiological

Table 7: Percent Error from Human Blood:Air and Tissue:Blood (Direct and PC_{EB} Equations) Algorithms

		Percent Error							
Tissue	**Chemical**	**A**	**B**	**D**	**F**	**G9**	**M**	**P6**	**T**
Blood:Air	Ethyl benzene	-47				27	2	-61	-72
	Toluene	-21				26	-34	-59	-49
	Trimethyl benzene, 1,2,3-	-56				17	22	-21	-78
	Trimethyl benzene, 1,2,4-	-66				6	27	-32	-85
	Trimethyl benzene, 1,3,5-	-62				31	68	-67	-83
	Xylene, m-	-52				9	-16	-60	-74
	Xylene, o-	-41				22	-12	-54	-66
	Xylene, p-	-65				-18	-36	-74	-81
Brain:Blood	Toluene	-46	-19	-10	-8		-55		-34
Fat:Blood	Ethyl benzene	41	-61	70			-4	8	7
	Toluene	-22	-75	28			-54	-18	-31
	Xylene, m-	22	-59	77			-18	17	-6
	Xylene, o-	9	-66	50			-28	13	-13
	Xylene, p-	7	-53	104			-27	-13	-18
Heart:Blood	Toluene		21						
Kidney:Blood	Toluene	-49	-13	33	26		-47		-38
Liver:Blood	Toluene	-72	-41	8	-21			-22	-48
	Xylene, m-	-67	34	122	4			40	-13
Lung:Blood	Toluene	-85	-50		-31				-63
Muscle:Blood	Toluene	-68	-39	-3	-17		-66	-13	

Note: A = Abraham *et al.* (1985) (E), B = Balaz and Lukacova (1999) (H), D = DeJongh *et al.* (1997) (H), F = Fiserova-Bergerova and Diaz (1986) (E), G9 = Gargas *et al.* (1989) (E), M = Meulenberg and Vijverberg (2000) (H), P6 = Poulin and Krishnan (1996a) (P), T = Tichy (1991) (E)

The values in Tables 6 and 7 vary widely (-99 to 480%) and do not give a good initial impression of algorithms used to calculate PCs. Table 8 provides perspective for evaluating these equations. Use of Table 8 is illustrated in the following example: for all blood:air and tissue:blood (direct and PC_{EB} equations) algorithms, 29% of the calculated values were within ±20% of the experimental value. Although Table 8 lists additional important percentages, attention is called to the ±20% minimum standard set in the Methods section due to normal levels of variability in biological data (Gearhart *et al.*, 1993).

Table 8: Percent of Blood:Air and Tissue:Blood (Direct and PC_{EB} Equations) Algorithms within ± Absolute Percent Error Levels

Model Type	Number of Calculations	Absolute Percent Error					
		10	**20**	**30**	**40**	**50**	**90**
All	231	15	**29**	42	54	65	90
Empirical	93	19	**30**	42	56	70	98
Hybrid	83	12	**28**	42	53	63	86
Physiological	55	13	**31**	40	51	60	86

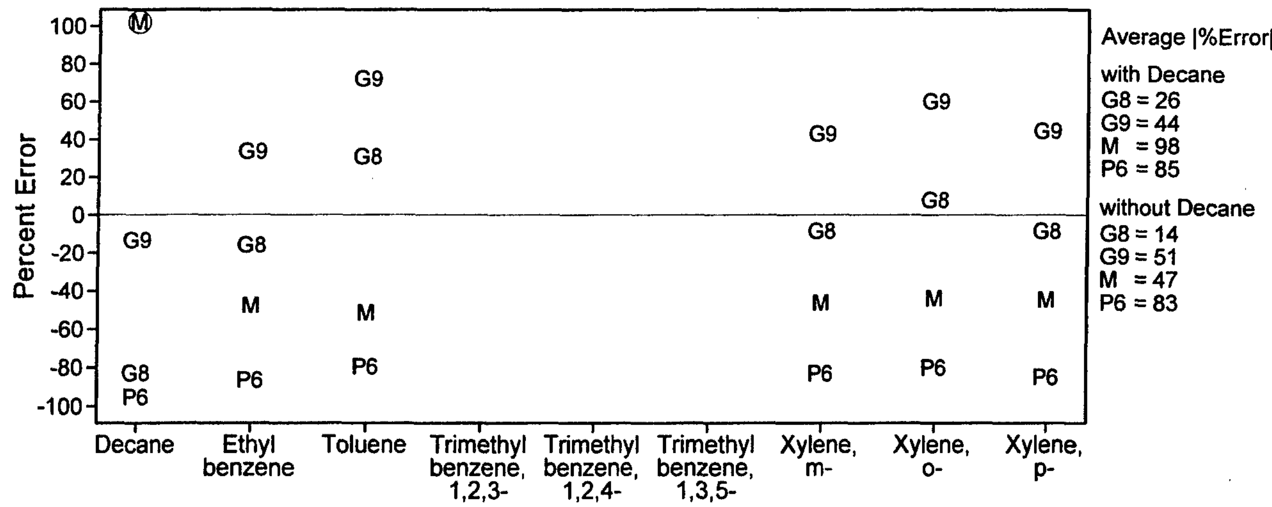
The type of equation did not affect the percentage of the calculations with values within 20% of experimental PCs; all types had nearly 30% of outcomes in this category. The type or basis of the algorithm appears to have little effect on accuracy of the outcome and no type of equation can be considered as better than another.

Performance by Tissue and/or Chemical

The algorithms were next evaluated on the basis of prediction adequacy for each tissue type.

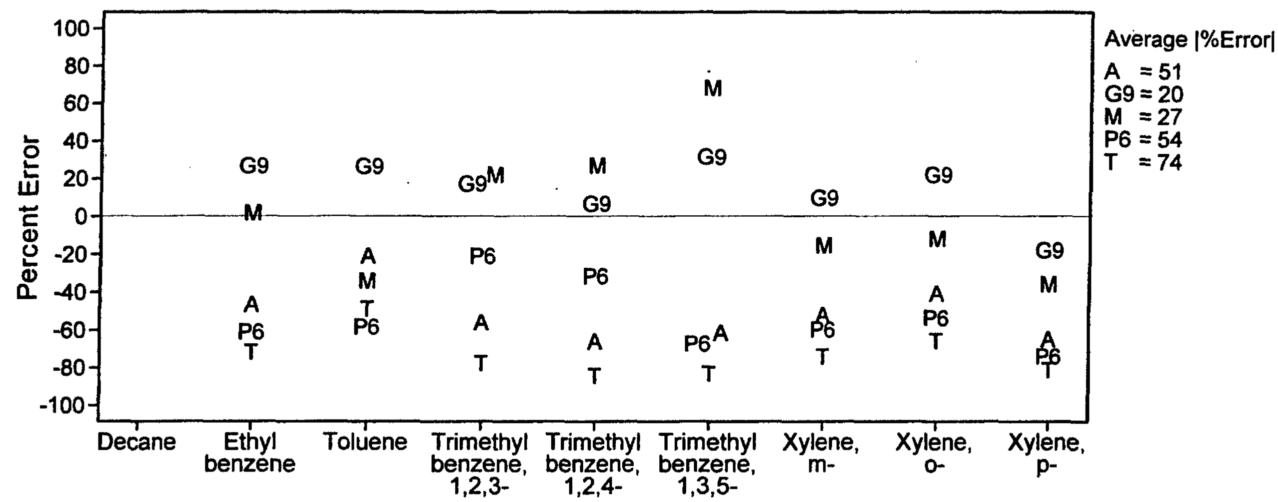
Blood:Air - Figures 1 and 2 depict the spread of predictions around the average experimental value for rat and human blood:air PCs, respectively. Each figure lists the average for each algorithm source at the right side. As there was a predicted value for decane rat blood:air PC, and as decane was the only alkane for which experimental values existed to facilitate comparison, two sets of averages are listed for Figure 1, with and without decane.

Figure 1: Percent Error for Each Estimate of Rat Blood:Air PCs Relative to Experimental Values



Notes: Circled letters = out of range (greater than 100% error), G8 = Gargas *et al.* (1988) (E), G9 = Gargas *et al.* (1989) (E), M = Meulenberg and Vijverberg (2000) (H), P6 = Poulin and Krishnan (1996a) (P), where (E) = empirical, (H) = hybrid and (P) = physiological

Figure 2: Percent Error for Each Estimate of Human Blood:Air PC Relative to Experimental Values



Notes: A= Abraham *et al.* (1985) (E), G9 = Gargas *et al.* (1989) (E), M = Meulenberg and Vijverberg (2000) (H), P6 = Poulin and Krishnan (1996a) (P), T = Tichy (1991) (E), where (E) = empirical, (H) = hybrid and (P) = physiological

Predicted rat blood:air PCs were best described by Gargas *et al.* (1988) (G8, Equation 6). The average absolute percent error for this source was 26% with decane (14% without). In addition,

values from this source had negative percent errors for some chemicals and positive for others, indicating that, for any new chemical similar to the ones used in this report, the result of this equation should fall near the experimental value and not be heavily skewed like some equations (P and M, Equations 3 and 4), resulting in consistent severe underprediction (Poulin and Krishnan, 1996a and Meulenberg and Vijverberg, 2000, respectively).

Average absolute percent error values decreased for three of the four sources of rat blood:air PC algorithms when the predicted decane value was removed. Only the Gargas *et al.* (1989) equation (G9, Equation 5) adequately predicted the blood:air PC for this alkane. Although the Gargas *et al.* (1989) equation performed better when alkanes were included, its overall averages were higher (|44%| with decane) than Gargas *et al.* (1988) (G8, Equation 6, |26%| with decane) and so would not be the best algorithm for this chemical set. Given the highly alkane composition of JP-8 (McDougal *et al.*, 2000), the algorithms evaluated here may not be appropriate for this task.

In comparing predicted rat and human blood:air PC distributions around the experimental values (Figures 1 and 2), the spread of percent error values is wider for predicted rat PCs while the spread for human percent errors is somewhat smaller. The differing success in predicting rat and human values is apparent when comparing equations from the same source (e.g., Gargas *et al.* (1989), G9, Equations 5 and 23). The greater difficulty in calculating rat blood:air PCs may be related to increased binding to proteins occurring in rat blood as compared to humans (Poulin and Krishnan, 1996b). Protein binding may also be a factor in why the physiological equations of Poulin and Krishnan (1996a) (P6, Equations 3 and 21) performed more poorly in predicting PCs for this medium (as compared to the empirical equations), as their approach does not incorporate a binding or correction term.

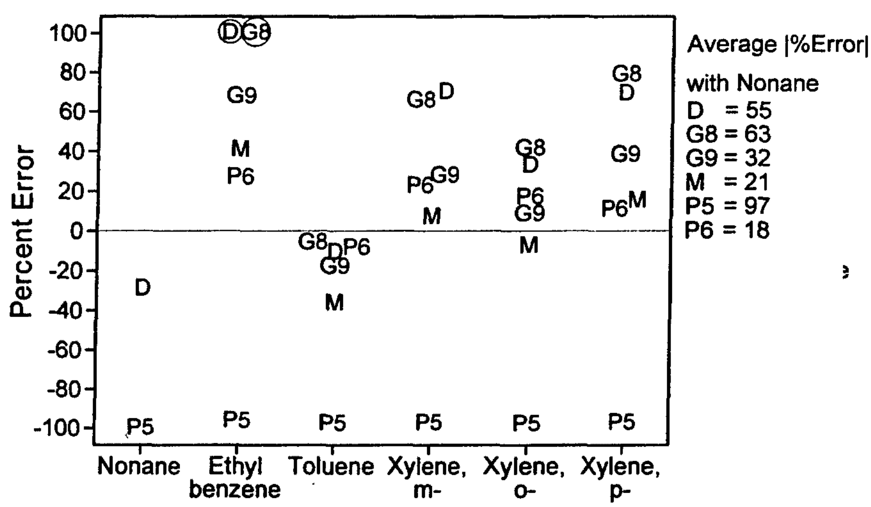
The human blood:air experimental PC values were best predicted by Gargas *et al.* (1989) (G9, Equation 23), with an average absolute percent error of 20%. The Meulenberg and Vijverberg (2000) equation (M, Equation 22) also did reasonably well with an average absolute value of 27%. Since experimental values for decane human blood:air PCs were not found, a comparison of predictions with and without an alkane was not possible.

Brain:Blood - Only one source, Meulenberg and Vijverberg (2000) (Equation 7), was found to provide a solvent-based brain:air equation with which to calculate a rat brain:blood PC_{EB}.

Therefore, no figure for comparison can be constructed. As seen in Table 6, percent error for individual estimates as compared to the experimental value varied widely from -23 to 480%; it is unlikely that this equation would be considered useful for modeling purposes for this set of chemicals. Conversely, only a single experimental value was found for blood:brain PCs in humans. Six different sources were located with algorithms for this parameter. With only a single predicted value each to compare with an experimental value (Table 7), no meaningful comparison of the algorithms can be discussed.

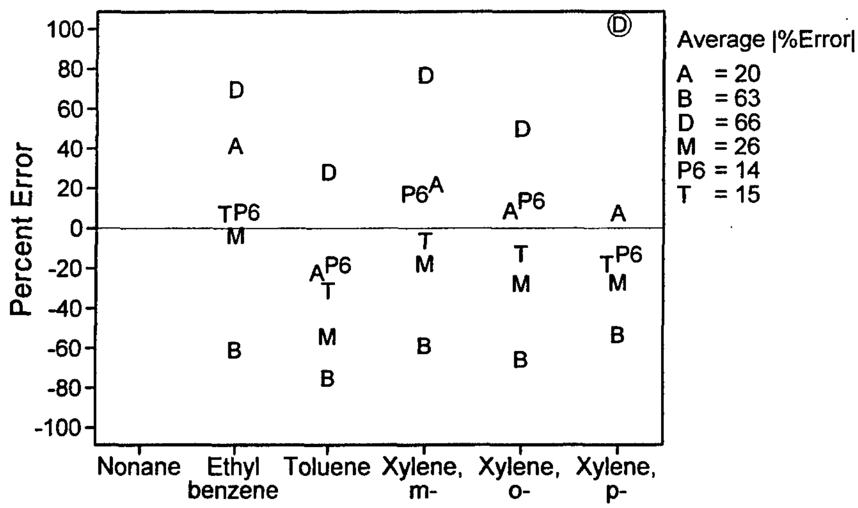
Fat:Blood - Figures 3 and 4 show the individual predictions around the experimental value for rat and human fat:blood PCs, respectively. These PCs were derived either from direct equations (Tables 4 and 5) or calculated from predicted tissue:air and experimental blood:air values (PC_{EB}, Tables 2 and 3). Averages for rat PCs again were listed with and without the available alkane, nonane. Human experimental values were not available for this chemical.

Figure 3: Percent Error (Relative to Experimental Values) for Each Estimate of Rat Fat:Blood PC (Direct and PC_{EB} Equations)



Notes: Circled letters = out of range (greater than 100% error); D = DeJongh *et al.* (1997) (H); G8 = Gargas *et al.* (1988) (E); G9 = Gargas *et al.* (1989) (E); M = Meulenberg and Vijverberg (2000) (H); P5 = Poulin and Krishnan (1995b) (P); P6 = Poulin and Krishnan (1996a) (P), where (E) = empirical, (H) = hybrid, (P) = physiological

Figure 4: Percent Error (Relative to Experimental Values) for Each Estimate of Human Fat:Blood PC (Direct and PC_{EB} Equations)



Notes: Circled letters = out of range (greater than 100% error), A = Abraham *et al.* (1985) (E); B = Balaz and Lukacova (1999) (H); D = DeJongh *et al.* (1997) (H); M = Meulenberg and Vijverberg (2000) (H); P6 = Poulin and Krishnan (1996a) (P); T = Tichy (1991) (E), where (E) = empirical, (H) = hybrid, (P) = physiological

For both rat and human fat:blood PCs, Poulin and Krishnan (1996a) (P6, Equations 8 and 29) performed best. Average absolute percent error in rat fat:blood PC predictions was 18%; since these are physiological equations, the tissue components appear to be most important in predicting the partitioning of chemicals in fat. In human predictions, Poulin and Krishnan (1996a) values averaged only 14% absolute percent error. Meulenberg and Vijverberg (2000) values (M, Equations 9 and 30) also performed well in both species, with average absolute percent errors of 21 and 26% for rat and human fat, respectively. Meulenberg and Vijverberg (2000) used hybrid equations that incorporated terms for tissue makeup. In humans, the Tichy (1991) equation (T, Equation 27) and the Abraham *et al.* (1985) (A, Equation 32) also performed well at 15% and 20% absolute percent error, respectively. Abraham *et al.* and Tichy both employed empirical equations generated from linear regressions.

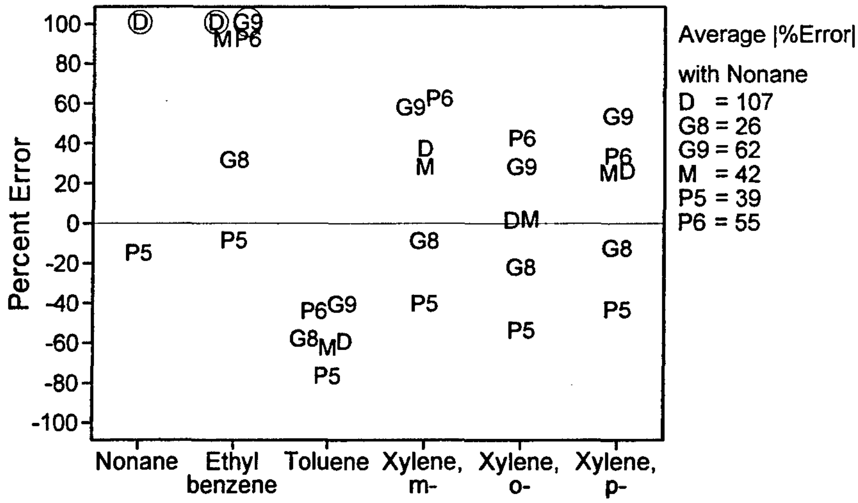
Appropriate solvent PCs were not available for decane to use all of the rat algorithms; only the two equations using octanol:water partitioning could be calculated for this compound. Therefore, the efficacy of these equations for alkane chemicals cannot be ascertained. No human experimental PCs for decane were found.

Heart:Blood - No heart:blood PC algorithms were found for rats. A single direct equation for heart:blood PC prediction was located for humans (Balaz and Lukacova, 1999, Equation 55). An experimental value for heart:blood PC was found for one chemical, toluene. Therefore a single prediction could be calculated, resulting in a 21% error as compared to the experimental number. No further comparisons can be made.

Kidney:Blood - A single source, Meulenberg and Vijverberg (2000) (Equation 12), was found to provide a solvent-based kidney:air equation with which to calculate a rat kidney:blood PC_{EB}. Compared with a single experimental value for toluene, this prediction was 234% different (Table 6). No further comparison can be constructed. Six sources were located providing algorithms for human kidney:air PCs. Again, only a single experimental value was found for blood:brain PCs in humans. With only a single predicted value each to compare with an experimental value (Table 7), no meaningful comparison of the algorithms can be discussed.

Liver:Blood - Figure 5 depicts the individual predictions around the experimental value for rat liver:blood PCs. These PCs were either direct or PC_{EB} calculated.

Figure 5: Percent Error (Relative to Experimental Values) for Each Estimate of Rat Liver:Blood PC (Direct and PC_{EB} Equations)



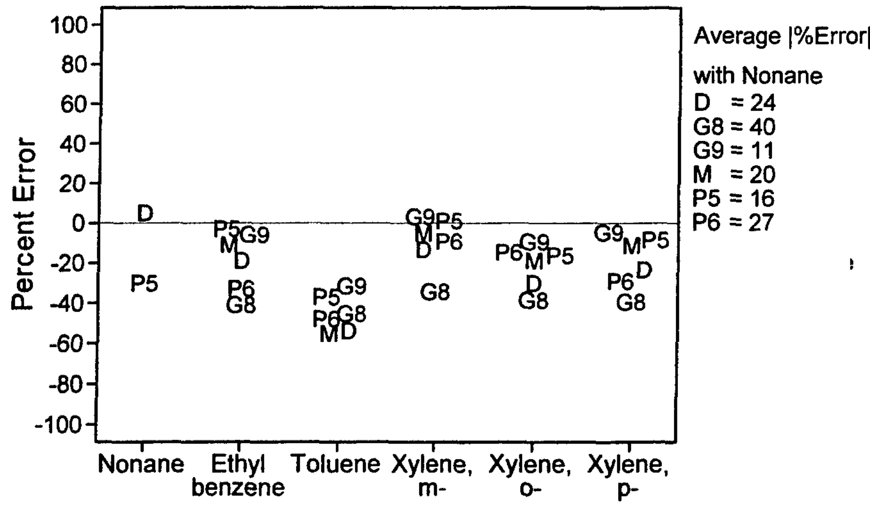
Notes: Circled letters = out of range (greater than 100% error), D = DeJongh *et al.* (1997) (H), G8 = Gargas *et al.* (1988) (E), G9 = Gargas *et al.* (1989) (E), M = Meulenberg and Vijverberg (2000) (H), P5 = Poulin and Krishnan (1995b) (P), P6 = Poulin and Krishnan (1996a) (P), where (E) = empirical, (H) = hybrid, (P) = physiological

For rat liver:blood PC predictions, Gargas *et al.* (1988) (G8, Equation 16) had the lowest average absolute percent error (26%) across the chemicals. Again, only the two equations using octanol:water partitioning could be calculated for this compound. Therefore, the efficacy of these equations for alkane chemicals can not be ascertained. Only two human experimental values for liver:blood PC were found, so a figure was not generated. With just two compounds for comparison (toluene and m-xylene), averages were not calculated. A study of Table 7 indicates that Fiserova-Bergerova and Diaz (1986, Equation 60) would have the lowest absolute percent error; however the experimental data are too limited to justify this conclusion.

Lung:Blood - Lung:blood PC algorithms were found only for humans. An experimental PC was located for toluene. The four algorithms ranged from -31 to -85% error (Table7). Further conclusions cannot be made.

Muscle:Blood - Figure 6 shows the spread of experimental values for rat muscle:blood PCs. Again, these PCs were either direct or PC_{EB} calculated.

Figure 6: Percent Error (Relative to Experimental Values) for Each Estimate of Rat Muscle:Blood PC (Direct and PC_{EB} Equations)



Notes: D = DeJongh *et al.* (1997) (H), G8 = Gargas *et al.* (1988) (E), G9 = Gargas *et al.* (1989) (E), M = Meulenberg and Vijverberg (2000) (H), P5 = Poulin and Krishnan (1995b) (P), P6 = Poulin and Krishnan (1996a) (P), where (E) = empirical, (H) = hybrid, (P) = physiological

Overall, rat muscle:blood PC tended to be underpredicted by algorithms. Several sources did adequate jobs of predicting this PC, judging by the average absolute percent errors, including Gargas *et al.* (1989) (G9, Equation 19) at 11%, Poulin and Krishnan (1995b) (P5, Equation 50) at 16% and Meulenberg and Vijverberg (2000) (M, Equation 18) at 20%.

Human experimental values for muscle:blood PC were limited to one, toluene. Six sources provided algorithms to calculate this PC. Percent errors ranged from -3 to -68% (Table 7).

A synopsis of conclusions that may be drawn following the tissue specific assessment of PC prediction algorithms can be found in Table 9 below. There were few tissues (four rat and two human) for which both experimental PC values and equations could be located to allow for meaningful comparison of the predictive algorithms.

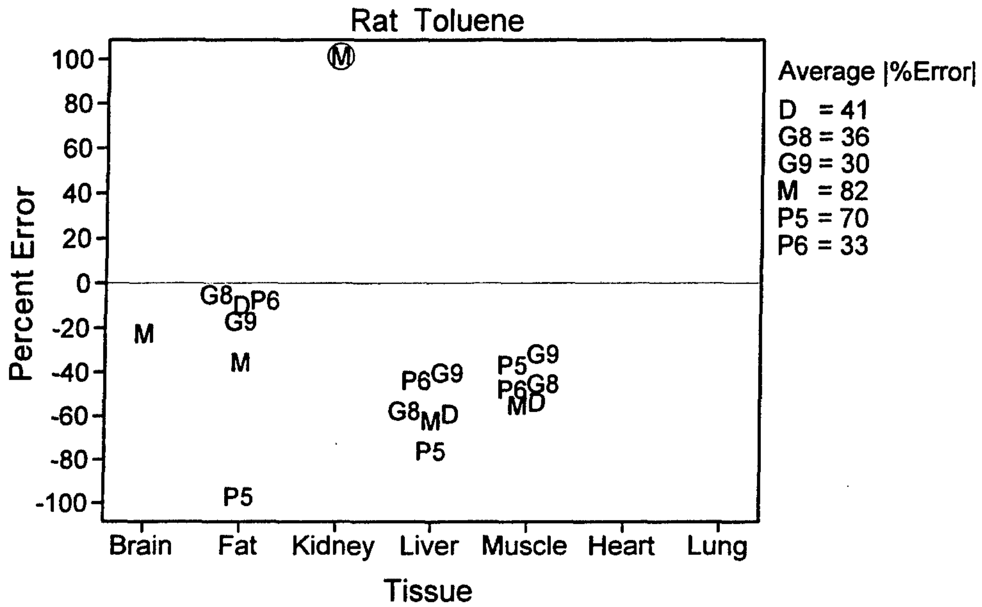
Table 9. Synopsis: Best Performance of Algorithms by Species and Organ for Solvent PC Based Equations

PC	Rat Best Equation for Chemical Set Based on Average |% Error|	Human Best Equation for Chemical Set Based on Average |% Error|
Blood:Air	**Gargas *et al.* (1988)** Equation 6 |26%| including alkanes |14%| excluding alkanes	**Gargas *et al.* (1989)** Equation 23 |20%| **Meulenberg and Vijverberg (2000)** Equation 22 |27%|
Brain:Blood	insufficient equations for comparison	insufficient experimental data for comparison
Fat:Blood	**Poulin and Krishnan (1996a)** Equation 8 |18%| **Meulenberg and Vijverberg (2000)** Equation 9 |21%|	**Poulin and Krishnan (1996a)** Equation 29 |14%| **Tichy (1991)** Equation 27 |15%| **Abraham *et al.* (1985)** Equation 32 |20%| **Meulenberg and Vijverberg (2000)** Equation 30 |26%|
Heart:Blood	no equation found	insufficient equations and experimental data for comparison
Kidney:Blood	insufficient equations for comparison	insufficient experimental data for comparison
Liver:Blood	**Gargas (1988)** Equation 16 |26%|	insufficient experimental data for comparison
Lung:Blood	no equation found	insufficient experimental data for comparison
Muscle Blood	**Gargas *et al.* (1989)** Equation 19 |11%| **Poulin and Krishnan (1995b)** Equation 50 |16%| **Meulenberg and Vijverberg (2000)** Equation 18 |20%|	insufficient experimental data for comparison

PCs for Toluene - To allow for a different perspective, a profile of predictions for a single chemical was considered for both rat and human tissues (Figures 7 and 8, respectively).

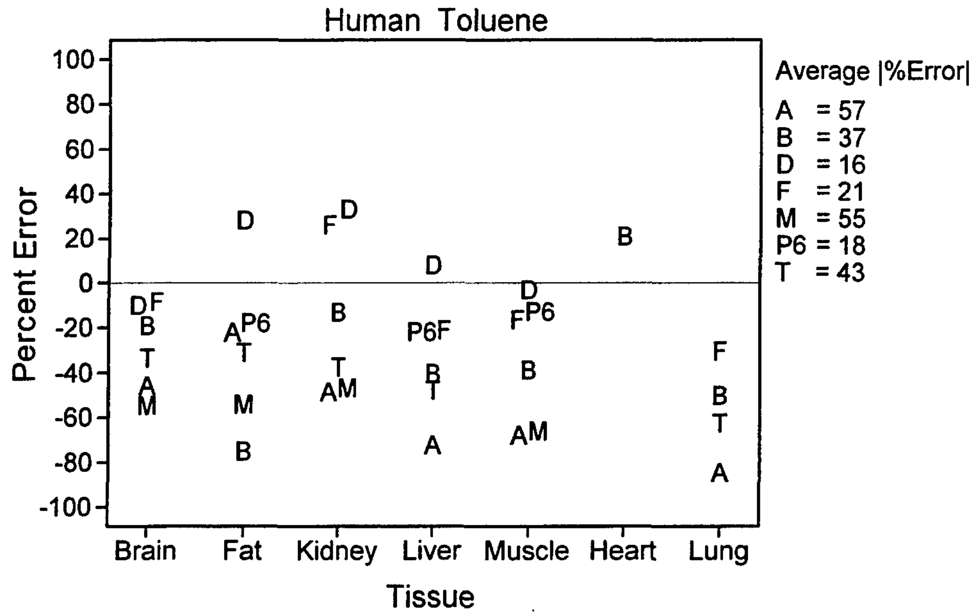
Toluene was chosen as it had the most complete list of experimental PC values. Overall performance was evaluated using the average absolute percent error for each source of algorithms; these percents are listed to the right of the figures.

Figure 7: Percent Error (Relative to Experimental Values) for Each Estimate of Rat Tissue:Blood PC (Direct and PC_{EB} Equations) for Toluene



Notes: Circled letters = out of range (greater than 100% error), D = DeJongh *et al.* (1997) (H), G8 = Gargas *et al.* (1988) (E), G9 = Gargas *et al.* (1989) (E), M = Meulenberg and Vijverberg (2000) (H), P5 = Poulin and Krishnan (1995b) (P), P6 = Poulin and Krishnan (1996a) (P), where (E) = empirical, (H) = hybrid, (P) = physiological

Figure 8: Percent Error (Relative to Experimental Values) for Each Estimate of Human Tissue:Blood PC (Direct and PC_{EB} Equations) for Toluene



Notes: A = Abraham *et al.* (1985) (E), B = Balaz and Lukacova (1999) (H), D = DeJongh *et al.* (1997) (H), F = Fiserova-Bergerova and Diaz (1986) (E), M = Meulenberg and Vijverberg (2000) (H), P6 = Poulin and Krishnan (1996a) (P), T = Tichy (1991) (E), where (E) = empirical, (H) = hybrid, (P) = physiological

A different picture is formed when looking at a single chemical rather than by tissue (Table 9). Algorithms from Gargas *et al.* (1989) performed "best" (lowest average absolute percent error, 30%) across rat tissues, while DeJongh *et al.* (1997) was "best" for human tissues (16%); Poulin and Krishnan (1996a) was the second "best source" for both species. In tissue by tissue comparisons above, Gargas *et al.* (1989) was found to be the best predictor for rat muscle:blood PCs but was not otherwise recommended in Table 9 for calculation of rat PC values. DeJongh *et al.* (1997) was not recommended in Table 9 for any of these tissues. Poulin and Krishnan (1996a) algorithms worked well only for fat:blood PC comparisons, in both rats and humans.

Performance of PC_{EB} versus PC_{PB} Equations

In this report, PC_{EB} values were first calculated because a PBPK modeler would use experimental blood:air numbers when these data were available. For many substances, however, blood:air partitioning experiments have not been performed or perhaps the results have not been published. Therefore, PC_{PB} values were also calculated by dividing predicted

tissue:air PCs by predicted blood:air PCs. A comparison of paired (same chemical, species, tissue and source of algorithms) PC_{EB} and PC_{PB} values are shown in Table 10.

Table 10: Comparison of PC_{EB} and PC_{PB} Tissue:Blood Values Calculated from the Same Algorithms for each Applicable Tissue and Chemical

Model Type	Number of Pairs	Percent of Pairs where Absolute Percent Error was less for PC_{EB} values compared with PC_{PB} values	Percentile of Relative Difference		
			Min	Median	Max
All	103	68	2	57	153
Empirical	51	55	7	35	137
Hybrid	29	66	2	58	70
Physiological	23	100	74	133	153

PC_{EB} values tended to be more accurate than PC_{PB} values overall. Of the 103 PC_{EB} and PC_{PB} paired equations, 68% had a smaller absolute percent error for the PC_{EB} value compared to the PC_{PB} value. Therefore, tissue:blood PCs calculated with experimental blood:air data, when available, are preferable over those calculated with predicted data for all equation types. However, 100% of PC_{EB} values from physiological equations had smaller absolute percent errors than their paired PC_{PB} values. This indicates that predicted blood:air values should not be used to substitute experimental blood:air data to calculate tissue:blood PCs from physiological equations.

In half of all pairs (i.e., median value), PC_{EB} and PC_{PB} values differed by less than 57%. The range of difference was between 2 and 153%, indicating that PC_{EB} and PC_{PB} predictions could be very similar or very different. Again, it is clear that the source of blood:air value used for calculating tissue:blood PCs from physiological equations is significant; PC_{EB} and PC_{PB} pairs were at least (i.e., minimum value) 74% different and ranged to 153% difference.

DISCUSSION

Tissue:blood and blood:air partition coefficients for each tissue compartment are essential to PBPK modeling (Gargas, 1991). Differences in tissue and blood PCs used in a PBPK model

can influence predictions (Jang *et al.*, 1999). Overall, solvent PC equations predicting rat and human blood:air PCs for selected JP-8 components were not consistent in their performance. Normal biological variation in blood:air partition coefficients has been observed at 20% (Gearhart *et al.*, 1993). Of all predictions (blood:air and direct or PC_{EB} tissue:blood), just 30% were within ±20% of experimental values. It is important to note that all types of equations (empirical, physiological or hybrid) performed equally well; roughly 30% of calculations from each type met the criterion (±20% of experimental value).

The complexity of the tissue in question appears to have some effect on which type of equation performs well in that tissue. Predictions for human blood:air PCs were more tightly clustered around the experimental values when contrasted with rat blood:air PCs (Figures 2 and 1, respectively); most likely the higher predictability in human blood is due to decreased capacity for reversible protein binding compared to rat blood (Poulin and Krishnan, 1996b). Human blood:air PCs were well predicted by two equations (Gargas *et al.* (1989), Equation 23, |20%|; Meulenberg and Vijverberg (2000), Equation 22, |27%|) whereas rat blood:air PCs were well predicted by a single equation (Gargas *et al.* (1988), Equation 6, |26%| including alkanes, |14%| excluding alkanes). These equations were either empirical or hybrid; all were derived from experimental data for low molecular weight volatiles. The majority of chemicals in this project were chemically similar (i.e., relatively small volatiles), making an empirical equation more likely to predict the experimental data well (Payne and Kenny, 2002).

Conversely, fat partitioning is relatively simple and does not involve significant binding. Fat:blood PCs are well modeled in both rats and humans by multiple equations (Table 9). The best of these were physiological equations (Poulin and Krishnan (1996a), Equations 8 and 29,|18%| and |14%|, respectively). The success of these algorithms suggests that fat partitioning depends largely on the composition of the tissue (fractions of neutral lipids, phospholipids and water) and not on additional factors that are compensated through regression in empirical and hybrid equations. Similarly, Poulin and Krishnan's (1995b) physiological equation performed reasonably well for rat muscle:blood PCs (Equation 50, |16%|). Fat has the highest neutral lipid and lowest water content of the tissues. Muscle has the lowest neutral lipid and highest water content (Poulin and Krishnan, 1996a). Physiological equations worked best for the two most differently composed tissues, but not for the tissues that are a heterogeneous mixture of lipids and water.

Tissue:air PCs, paired with a blood:air PC for the same chemical, tissue and species, are used to calculate a tissue:blood PC using Equation 1 (Fiserova-Bergerova, 1983; Poulin and Krishnan, 1995a). Using experimental blood:air PCs (PC_{EB}) for this calculation is preferable since 68% of PC_{EB} values generated were closer to experimental data values (smaller absolute percent errors) than their counterparts that were calculated from predicted blood:air PC values (PC_{PB}) (Table 10). Unfortunately, experimental blood:air values are not always available in the literature. Although vial equilibration studies for volatile chemicals are not difficult or expensive, nonvolatile chemicals require expensive radiolabeled compounds or animal intensive testing to determine PCs experimentally (Murphy *et al.*, 1995; Poulin and Krishnan, 1995a). In these cases, PC_{PB} values may be calculated using physiological equations, but caution should be used in interpreting the results since 100% of the physiological PC_{PB} values were farther from experimental data as compared to their experimentally-based PC_{EB} counterparts.

Due to lack of solvent PCs for nonane and decane, only one comparison was possible to determine if tissue:blood PC algorithms were suitable for alkanes. Average rat blood:air PCs were adversely affected by the inclusion of the alkane, decane, with the exception of Gargas *et al.* (1989) (Equation 5, |44% | with alkanes, |51%| without alkanes). Another Gargas *et al.* equation (1988, Equation 6) performed better (|26%| including alkanes, |14%| excluding alkanes). In general, empirical and hybrid equations will predict better for chemicals similar to those for which the equation was derived (Payne and Kenny, 2002) and are of limited predictive value beyond these chemical families because they do not incorporate mechanistic terms for partitioning (Poulin and Krishnan, 1996c). The results of this with alkane vs. no alkane comparison raise doubts as to whether the solvent PC based algorithms evaluated in this project are appropriate for the task of calculating tissue and blood PCs for JP-8 components, which are largely alkanes (McDougal *et al.*, 2000).

A major limitation encountered in this project was the lack of experimental data for the selected JP-8 constituents. This deficit included solvent PCs, rat tissue and blood PCs and especially human tissue and blood PCs for these chemicals of concern. As a result, predictive algorithms for only four rat and two human tissues (blood included) were able to be adequately evaluated in Table 9. Unfortunately, this lack of experimental data is the reality for scientists wishing to model petroleum based mixtures. The most prevalent compound (undecane, Table 1, McDougal *et al.*, 2000) in JP-8 is one for which there is no published tissue or blood partition

information; however, these PC experiments in rat tissues are in progress at the University of Georgia (Fisher, personal communication, 2003).

Although the lack of experimental tissue and blood PCs for these chemicals is still a concern, additional non-solvent PC based algorithms are available that may result in better predictions of experimental tissue PC data. These algorithms, however, were outside the scope of this project. Alternative algorithms use chemical solubilities (Paterson and Mackay, 1989; Poulin and Krishnan, 1996c) or other physical properties such as geometric volume (Beliveau and Krishnan, 2000).

CONCLUSIONS

Overall, the ability of all three types of equations (Tables 2 through 5) to predict blood:air and tissue:blood partition coefficients, both necessary to PBPK modeling, was limited. Use of calculated PCs from solvent partitioning equations should be carefully considered. For the purpose of this project, use of experimental PCs (Tables A-2 and A-3) in the JP-8 mixture model is recommended whenever available. The algorithms shown in Table 9 may be used when experimental data are not available. For all applications, if calculated PC values must be used, a comparison of experimental and predicted PCs for chemically similar compounds is advisable. This allows the PBPK modeler to account for the variability and uncertainty inherent in the partition coefficient used.

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APPENDIX A

Table A-1. Solvent Partition Coefficients for Select List of JP-8 Components

Chemical	Temp (°C)	Oil:Air	Saline:Air, Water:Air	log Octanol:Water	Source or Method	Reference
Decane	37	14400	0.0041		vial equilibration	Taheri *et al.*, 1993
Decane	25			5.01	lit., avg. value	Verbruggen *et al.*, 2000; Yaws *et al.*, 1999
Dimethyl naphthalene, 1,2-	25			4.31	lit., avg. value	Gute and Basajm 2001; Yaws *et al.*, 1999
Dimethyl naphthalene, 1,3-	25			4.42	lit., avg. value	Gute and Basak, 2001; Yaws *et al.*, 1999
Dimethyl naphthalene, 1,4-	25			4.37	lit., avg. value	Gute and Basak, 2001; Yaws *et al.*, 1999
Dimethyl naphthalene, 1,5-	25			4.38	lit., avg. value	Gute and Basak, 2001; Yaws *et al.*, 1999
Dimethyl naphthalene, 1,6-	25			4.26	lit.	Yaws *et al.*, 1999
Dimethyl naphthalene, 1,7-	25			4.44	lit., avg. value	Gute and Basak, 2001; Yaws *et al.*, 1999
Dimethyl naphthalene, 1,8-	NA			4.26	lit.	Gute and Basak, 2001
Dimethyl naphthalene, 2,3-	25			4.37	lit., avg. value	Gute and Basak, 2001; Yaws *et al.*, 1999
Dimethyl naphthalene, 2,6-	NA			4.31	lit.	Gute and Basak, 2001
Dimethyl naphthalene, 2,7-	25			4.26	lit.	Yaws *et al.*, 1999
Dodecane	25			5.95	lit., avg. value	Verbruggen *et al.*, 2000; Yaws *et al.*, 1999
Ethyl benzene	25			3.15	lit., avg. value	Gute and Basak, 2001; Yaws *et al.*, 1999
Ethyl benzene	37	3791	1.69		vial equilibration	Sato and Nakajima, 1979
Methyl naphthalene, 1-	25			3.87	lit., avg. value	Gute and Basak, 2001; Yaws *et al.*, 1999
Methyl naphthalene, 2-	25			3.86	lit., avg. value	Gute and Basak, 2001; Yaws *et al.*, 1999
Naphthalene	25			3.35	lit., avg. value	Beyer *et al.*, 2002; de Maagd *et al.*, 1998; Gute and Basak, 2001; Sartorelli *et al.*, 1998; Yaws *et al.*, 1999
Nonane	25			4.635	lit., avg. value	Verbruggen *et al.*, 2000; Yaws *et al.*, 1999

Chemical	Temp (°C)	Oil:Air	Saline:Air, Water:Air	log Octanol:Water	Source or Method	Reference
Pentadecane	25			7.71	lit.	Yaws *et al.*, 1999
Tetradecane	25			7.2	lit.	Verbruggen *et al.*, 2000; Yaws *et al.*, 1999
Toluene	37	1056	1.99		vial equilibration, avg. value	Gargas *et al.*, 1989; Sato and Nakajima, 1979
Toluene	25			2.73	lit., avg. value	Gute and Basak, 2001; Yaws *et al.*, 1999
Toluene	37			2.65	lit.	Poulin and Krishnan, 1995b
Trimethyl benzene, 1,2,3-	25			3.66	lit., avg. value	Gute and Basak, 2001; Yaws *et al.*, 1999
Trimethyl benzene, 1,2,3-	37	10900	2.73		lit.	Jarnberg and Johanson, 1995
Trimethyl benzene, 1,2,4-	25			3.78	lit., avg. value	Gute and Basak, 2001; Yaws *et al.*, 1999
Trimethyl benzene, 1,2,4-	37	10200	1.61		lit.	Jarnberg and Johanson, 1995
Trimethyl benzene, 1,3,5-	NA			3.42	lit.	Gute and Basak, 2001
Trimethyl benzene, 1,3,5-	37	9880	1.23		lit.	Jarnberg and Johanson, 1995
Undecane	25			5.74	lit.	Yaws *et al.*, 1999
Xylene - m	37	3543.5	1.79		vial equilibration, avg. value	Gargas *et al.*, 1989; Sato and Nakajima, 1979
Xylene - m	25			3.2	lit., avg. value	Gargas *et al.*, 1989; Yaws *et al.*, 1999
Xylene - o	37	3947	2.64		vial equilibration, avg. value	Gargas *et al.*, 1989; Sato and Nakajima, 1979
Xylene - o	25			3.12	lit., avg. value	Gute and Basak, 2001; Yaws *et al.*, 1999
Xylene - p	37	3506.5	1.67		vial equilibration, avg. value	Gargas *et al.*, 1989; Sato and Nakajima, 1979
Xylene - p	25			3.15	lit., avg. value	Gute and Basak, 2001; Yaws *et al.*, 1999

avg. - average, lit. - literature value

NA - not applicable - The temperature dependence of log P is very small (Leo, personal communication, 2003); however, value is same as or similar to 25°C value in most of the instances when used in an average.

Table A-2. Published Rat Tissue and Blood Partition Coefficients for Select JP-8 Components

Chemical	Tissue or Blood	Blood:Air	Tissue:Blood	Method	Reference
Decane	Blood	17.3		closed chamber	Liu *et al.*, 1994
Ethyl benzene	Blood (projected fr. avg. diff. btw. 250 g and 350 g rats in xylenes)	44.40			
Ethyl benzene	Brain (back-calc. using 44.4 projected fr. bl:air avg. in xylenes)		0.80	vial equilibration	Kumarathasan *et al.*, 1998
Ethyl benzene	Fat (back-calc. using 44.4 projected fr. bl:air avg. in xylenes)		36.00	vial equilibration	Kumarathasan *et al.*, 1998
Ethyl benzene	Kidney (back-calc. using 44.4 projected fr. bl:air avg. in xylenes)		0.70	vial equilibration	Kumarathasan *et al.*, 1998
Ethyl benzene	Liver (back-calc. using 44.4 projected fr. bl:air avg. in xylenes)		1.20	vial equilibration	Kumarathasan *et al.*, 1998
Ethyl benzene	Muscle (back-calc. using 44.4 projected fr. bl:air avg. in xylenes)		1.00	vial equilibration	Kumarathasan *et al.*, 1998
Nonane	Blood	5.13		vial equilibration	Robinson, 2000
Nonane	Brain		5.04	vial equilibration	Robinson, 2000
Nonane	Fat		244.44	vial equilibration	Robinson, 2000
Nonane	Liver		1.29	vial equilibration	Robinson, 2000
Nonane	Muscle		1.39	vial equilibration	Robinson, 2000
Toluene	Blood	18.00		vial equilibration	Gargas *et al.*, 1989
Toluene	Brain		4.22	lit. source	Fiserova-Bergerova, 1983
Toluene	Fat		55.00	vial equilibration	Gargas *et al.*, 1989; Pierce *et al.*, 1996
Toluene	Heart		3.75	lit. source	Fiserova-Bergerova, 1983
Toluene	Kidney		4.69	lit. source	Fiserova-Bergerova, 1983
Toluene	Liver		4.64	vial equilibration	Gargas *et al.*, 1989
Toluene	Lung		4.53	lit. source	Fiserova-Bergerova, 1983
Toluene	Muscle		1.54	vial equilibration	Gargas *et al.*, 1989
Xylene - m	Blood - Average All	42.07		vial equilibration; lit. source	Gargas *et al.*, 1989; Kaneko *et al.*, 2000a; Kumarathasan *et al.*, 1998

Chemical	Tissue or Blood	Blood:Air	Tissue:Blood	Method	Reference
Xylene - m	Blood - Average Experimental	40.76		vial equilibration	Gargas *et al.*, 1989; Kumarathasan *et al.*, 1998
Xylene - m	Brain (back-calculation)		1.20	vial equilibration	Kumarathasan *et al.*, 1998
Xylene - m	Fat - Average All		49.05	vial equilibration; lit. source	Gargas *et al.*, 1989; Kaneko *et al.*, 2000a; Kumarathasan *et al.*, 1998; Pierce *et al.*, 1996
Xylene - m	Fat - Average Experimental		48.23	vial equilibration	Gargas *et al.*, 1989; Kumarathasan *et al.*, 1998; Pierce *et al.*, 1996
Xylene - m	Kidney (back-calculation)		1.00	vial equilibration	Kumarathasan *et al.*, 1998
Xylene - m	Liver - Average All		1.89	vial equilibration; lit. source	Gargas *et al.*, 1989; Kaneko *et al.*, 2000a; Kumarathasan *et al.*, 1998
Xylene - m	Liver - Average Experimental		1.84	vial equilibration	Gargas *et al.*, 1989; Kumarathasan *et al.*, 1998
Xylene - m	Lung (back-calculation)		2.71	lit. source	Kaneko *et al.*, 2000a
Xylene - m	Muscle - Average All		1.30	vial equilibration; lit. source	Gargas *et al.*, 1989; Kaneko *et al.*, 2000a; Kumarathasan *et al.*, 1998
Xylene - m	Muscle - Average Experimental		0.96	vial equilibration	Gargas *et al.*, 1989; Kumarathasan *et al.*, 1998
Xylene - m	Richly Perfused - Average All		1.72	vial equilibration; lit. source	Kaneko *et al.*, 2000a; Kaneko *et al.*, 2000b
Xylene - m	Richly Perfused - Average Experimental		1.11	vial equilibration	Kaneko *et al.*, 2000b
Xylene - o	Blood - Average All	43.30		vial equilibration, back-calculation	Gargas *et al.*, 1989
Xylene - o	Blood - Average Experimental	44.30		vial equilibration	Gargas *et al.*, 1989
Xylene - o	Brain (back-calc. using 42.3 projected fr. bl:air avg. in xylenes)		1.70	vial equilibration	Kumarathasan *et al.*, 1998
Xylene - o	Fat - Average Experimental		57.01	vial equilibration	Gargas *et al.*, 1989; Kumarathasan *et al.*, 1998; Pierce *et al.*, 1996
Xylene - o	Kidney (back-calc. using 42.3 projected fr. bl:air avg. in xylenes)		1.50	vial equilibration	Kumarathasan *et al.*, 1998
Xylene - o	Liver - Average Experimental		2.37	vial equilibration	Gargas *et al.*, 1989; Kumarathasan *et al.*, 1998
Xylene - o	Muscle - Average Experimental		1.16	vial equilibration	Gargas *et al.*, 1989; Kumarathasan *et al.*, 1998

Chemical	Tissue or Blood	Blood:Air	Tissue:Blood	Method	Reference
Xylene - p	Blood - Average Experimental	39.15		vial equilibration	Gargas *et al.*, 1989; Kumarathasan *et al.*, 1998
Xylene - p	Brain		1.20	vial equilibration	Kumarathasan *et al.*, 1998
Xylene - p	Fat - Average Experimental		46.16	vial equilibration	Gargas *et al.*, 1989; Kumarathasan *et al.*, 1998
Xylene - p	Kidney		1.00	vial equilibration	Kumarathasan *et al.*, 1998
Xylene - p	Liver - Average Experimental		1.94	vial equilibration	Gargas *et al.*, 1989; Kumarathasan *et al.*, 1998
Xylene - p	Muscle - Average Experimental		1.06	vial equilibration	Gargas *et al.*, 1989; Kumarathasan *et al.*, 1998

avg. - average; bl - blood; btw. - between; calc. - calculation; diff. - difference; fr. - from

Table A-3. Published Human Tissue and Blood Partition Coefficients for Select JP-8 Components

Chemical	Tissue or Blood	Blood:Air	Tissue:Blood	Method	Reference
Ethyl benzere	Blood	28.40		lit. source	Fiserova-Bergerova, 1983
Ethyl benzere	Fat		62.11	vial equilibration	Pierce *et al.*, 1996
Toluene	Blood - Experimental	14.30		vial equilibration	Fiserova-Bergerova *et al.*, 1984; Pierce *et al.*, 1996
Toluene	Blood - Average All	14.72		vial equilibration; lit. sources	Fiserova-Bergerova, 1983, Fiserova-Bergerova *et al.*, 1984; Pierce *et al.*, 1996
Toluene	Brain		3.53	vial equilibration	Fiserova-Bergerova *et al.*, 1984
Toluene	Fat - Experimental		72.98	vial equilibration	Fiserova-Bergerova *et al.*, 1984; Pierce *et al.*, 1996
Toluene	Fat - Average All		74.65	vial equilibration; lit. sources	Fiserova-Bergerova, 1983; Pierce *et al.*, 1996; Tardif *et al.*, 1995
Toluene	Heart		2.01	lit. source	Fiserova-Bergerova, 1983
Toluene	Kidney		1.73	vial equilibration	Fiserova-Bergerova *et al.*, 1984
Toluene	Liver - Average All		3.83	lit. sources	Fiserova-Bergerova *et al.*, 1984; Tardif *et al.*, 1995
Toluene	Liver - Experimental		4.68	vial equilibration	Fiserova-Bergerova *et al.*, 1984
Toluene	Lung		2.03	vial equilibration	Fiserova-Bergerova *et al.*, 1984
Toluene	Muscle		3.39	vial equilibration	Fiserova-Bergerova *et al.*, 1984
Toluene	Richly Perfused		2.66	lit. sources	Tardif *et al.*, 1995
Toluene	Slowly Perfused		1.37	lit. sources	Tardif *et al.*, 1995
Trimethyl benzene, 1,2,3-	Blood	66.50		vial equilibration	Jarnberg and Johanson, 1995
Trimethyl benzene, 1,2,4-	Blood	59.10		vial equilibration	Jarnberg and Johanson, 1995
Trimethyl benzene, 1,3,5-	Blood	43.00		vial equilibration	Jarnberg and Johanson, 1995
Xylene - m	Blood - Average Experimental	32.20		vial equilibration	Fiserova-Bergerova, 1983; Gargas *et al.*, 1989; Pierce *et al.*, 1996
Xylene - m	Blood - Average All	32.27		vial equilibration; lit. sources	Fiserova-Bergerova, 1983; Gargas *et al.*, 1989; Pierce *et al.*, 1996
Xylene - m	Fat - Experimental		60.16	vial equilibration	Pierce *et al.*, 1996
Xylene - m	Fat - Average All		68.98	vial equilibration; lit. sources	Pierce *et al.*, 1996; Tardif *et al.*, 1995
Xylene - m	Liver		3.02	lit. sources	Tardif *et al.*, 1995
Xylene - m	Richly Perfused		4.42	lit. sources	Tardif *et al.*, 1995
Xylene - m	Slowly Perfused		3.00	lit. sources	Tardif *et al.*, 1995

Chemical	Tissue or Blood	Blood:Air	Tissue:Blood	Method	Reference
Xylene - o	Blood - Average All	33.73		vial equilibration; lit. sources	Fiserova-Bergerova, 1983; Gargas *et al.*, 1989; Pierce *et al.*, 1996
Xylene - o	Blood - Average Experimental	35.05		vial equilibration	Gargas *et al.*, 1989; Pierce *et al.*, 1996
Xylene - o	Fat		69.89	vial equilibration	Pierce *et al.*, 1996
Xylene - p	Blood - Average Experimental	41.85		vial equilibration	Gargas *et al.*, 1989; Pierce *et al.*, 1996
Xylene - p	Fat		51.77	vial equilibration	Pierce *et al.*, 1996

APPENDIX B

Table B-1. Results of Algorithms for Rat Blood:Air and Tissue:Blood (Direct, PC_{EB} and PC_{PB}) PC Values

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
Blood:Air	Decane	E	Gargas *et al.*, 1988		17.30	2.97	-82.86	83
Blood:Air	Decane	E	Gargas *et al.*, 1989		17.30	14.99	-13.38	13
Blood:Air	Decane	H	Meulenberg and Vijverberg, 2000		17.30	78.92	356.21	356
Blood:Air	Decane	P	Poulin and Krishnan, 1996a		17.30	0.80	-95.37	95
Blood:Air	Ethyl benzene	E	Gargas *et al.*, 1988		44.40	37.32	-15.95	16
Blood:Air	Ethyl benzene	E	Gargas *et al.*, 1989		44.40	59.30	33.55	34
Blood:Air	Ethyl benzene	H	Meulenberg and Vijverberg, 2000		44.40	23.20	-47.74	48
Blood:Air	Ethyl benzene	P	Poulin and Krishnan, 1996a		44.40	5.96	-86.58	87
Blood:Air	Toluene	E	Gargas *et al.*, 1988		18.00	23.55	30.83	31
Blood:Air	Toluene	E	Gargas *et al.*, 1989		18.00	30.97	72.07	72
Blood:Air	Toluene	H	Meulenberg and Vijverberg, 2000		18.00	8.72	-51.58	52
Blood:Air	Toluene	P	Poulin and Krishnan, 1996a		18.00	3.70	-79.42	79
Blood:Air	Xylene - m	E	Gargas *et al.*, 1988		40.76	37.35	-8.37	8
Blood:Air	Xylene - m	E	Gargas *et al.*, 1989		40.76	58.29	43.01	43
Blood:Air	Xylene - m	H	Meulenberg and Vijverberg, 2000		40.76	21.96	-46.12	46
Blood:Air	Xylene - m	P	Poulin and Krishnan, 1996a		40.76	6.90	-83.08	83
Blood:Air	Xylene - o	E	Gargas *et al.*, 1988		44.30	47.77	7.83	8

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
Blood:Air	Xylene - o	E	Gargas *et al.*, 1989		44.30	70.91	60.07	60
Blood:Air	Xylene - o	H	Meulenberg and Vijverberg, 2000		44.30	24.93	-43.72	44
Blood:Air	Xylene - o	P	Poulin and Krishnan, 1996a		44.30	8.83	-80.06	80
Blood:Air	Xylene - p	E	Gargas *et al.*, 1988		39.15	35.88	-8.36	8
Blood:Air	Xylene - p	E	Gargas *et al.*, 1989		39.15	56.56	44.46	44
Blood:Air	Xylene - p	H	Meulenberg and Vijverberg, 2000		39.15	21.65	-44.70	45
Blood:Air	Xylene - p	P	Poulin and Krishnan, 1996a		39.15	5.89	-84.96	85
Brain:Blood	Ethyl benzene	H	Meulenberg and Vijverberg, 2000	EB	0.80	4.64	93	93
Brain:Blood	Ethyl benzene	H	Meulenberg and Vijverberg, 2000	PB	0.80	8.88	2	2
Brain:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	EB	4.22	3.26	1336	1336
Brain:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	PB	4.22	6.73	-22	22
Brain:Blood	Xylene - m	H	Meulenberg and Vijverberg, 2000	EB	1.20	4.73	413	413
Brain:Blood	Xylene - m	H	Meulenberg and Vijverberg, 2000	PB	1.20	8.78	-28	28
Brain:Blood	Xylene - o	H	Meulenberg and Vijverberg, 2000	EB	1.70	4.86	-15	15
Brain:Blood	Xylene - o	H	Meulenberg and Vijverberg, 2000	PB	1.70	8.64	28	28
Brain:Blood	Xylene - p	H	Meulenberg and Vijverberg, 2000	EB	1.20	4.87	-59	59
Brain:Blood	Xylene - p	H	Meulenberg and Vijverberg, 2000	PB	1.20	8.81	-20	20

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
FatBlood	Ethyl benzene	H	DeJongh *et al.*, 1997	D	36.00	78.44	480	480
FatBlood	Ethyl benzene	E	Gargas *et al.*, 1988	EB	36.00	79.16	27	27
FatBlood	Ethyl benzene	E	Gargas *et al.*, 1988	PB	36.00	94.19	66	66
FatBlood	Ethyl benzene	E	Gargas *et al.*, 1989	EB	36.00	60.65	66	66
FatBlood	Ethyl benzene	E	Gargas *et al.*, 1989	PB	36.00	45.41	591	591
FatBlood	Ethyl benzene	H	Meulenberg and Vijverberg, 2000	EB	36.00	50.93	-58	58
FatBlood	Ethyl benzene	H	Meulenberg and Vijverberg, 2000	PB	36.00	97.45	2	2
FatBlood	Ethyl benzene	P	Poulin and Krishnan, 1995b	D	36.00	1.56	-30	30
FatBlood	Ethyl benzene	P	Poulin and Krishnan, 1996a	EB	36.00	45.90	-13	13
FatBlood	Ethyl benzene	P	Poulin and Krishnan, 1996a	PB	36.00	342.07	-19	19
FatBlood	Nonane	H	DeJongh *et al.*, 1997	D	244.44	175.17	1010	1010
FatBlood	Nonane	P	Poulin and Krishnan, 1995b	D	244.44	1.56	-11	11
FatBlood	Toluene	H	DeJongh *et al.*, 1997	D	55.00	49.44	-23	23
FatBlood	Toluene	E	Gargas *et al.*, 1988	EB	55.00	52.15	850	850
FatBlood	Toluene	E	Gargas *et al.*, 1988	PB	55.00	39.86	82	82
FatBlood	Toluene	E	Gargas *et al.*, 1989	EB	55.00	45.51	-97	97
FatBlood	Toluene	E	Gargas *et al.*, 1989	PB	55.00	26.45	390	390
FatBlood	Toluene	H	Meulenberg and Vijverberg, 2000	EB	55.00	35.38	-68	68

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
FatBlood	Toluene	H	Meulenberg and Vijverberg, 2000	PB	55.00	73.07	82	82
FatBlood	Toluene	P	Poulin and Krishnan, 1995b	D	55.00	1.55	70	70
FatBlood	Toluene	P	Poulin and Krishnan, 1996a	EB	55.00	50.69	-34	34
FatBlood	Toluene	P	Poulin and Krishnan, 1996a	PB	55.00	246.29	44	44
FatBlood	Xylene - m	H	DeJongh *et al.*, 1997	D	48.23	82.31	60	60
FatBlood	Xylene - m	E	Gargas *et al.*, 1988	EB	48.23	80.25	-28	28
FatBlood	Xylene - m	E	Gargas *et al.*, 1988	PB	48.23	87.57	28	28
FatBlood	Xylene - m	E	Gargas *et al.*, 1989	EB	48.23	61.95	18	18
FatBlood	Xylene - m	E	Gargas *et al.*, 1989	PB	48.23	43.32	810	810
FatBlood	Xylene - m	H	Meulenberg and Vijverberg, 2000	EB	48.23	51.88	-41	41
FatBlood	Xylene - m	H	Meulenberg and Vijverberg, 2000	PB	48.23	96.28	-54	54
FatBlood	Xylene - m	P	Poulin and Krishnan, 1995b	D	48.23	1.56	-3	3
FatBlood	Xylene - m	P	Poulin and Krishnan, 1996a	EB	48.23	59.42	-28	28
FatBlood	Xylene - m	P	Poulin and Krishnan, 1996a	PB	48.23	351.18	-17	17
FatBlood	Xylene - o	H	DeJongh *et al.*, 1997	D	57.01	76.15	294	294
FatBlood	Xylene - o	E	Gargas *et al.*, 1988	EB	57.01	81.02	-99	99
FatBlood	Xylene - o	E	Gargas *et al.*, 1988	PB	57.01	75.13	-10	10
FatBlood	Xylene - o	E	Gargas *et al.*, 1989	EB	57.01	62.21	490	490
FatBlood	Xylene - o	E	Gargas *et al.*, 1989	PB	57.01	38.86	403	403
FatBlood	Xylene - o	H	Meulenberg and Vijverberg, 2000	EB	57.01	53.14	-66	66
FatBlood	Xylene - o	H	Meulenberg and Vijverberg, 2000	PB	57.01	94.42	43	43

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
FatBlood	Xylene - o	P	Poulin and Krishnan, 1995b	D	57.01	1.56	-33	33
FatBlood	Xylene - o	P	Poulin and Krishnan, 1996a	EB	57.01	67.07	4	4
FatBlood	Xylene - o	P	Poulin and Krishnan, 1996a	PB	57.01	336.33	-15	15
FatBlood	Xylene - p	H	DeJongh *et al.*, 1997	D	46.16	78.44	632	632
FatBlood	Xylene - p	E	Gargas *et al.*, 1988	EB	46.16	82.91	-10	10
FatBlood	Xylene - p	E	Gargas *et al.*, 1988	PB	46.16	90.47	8	8
FatBlood	Xylene - p	E	Gargas *et al.*, 1989	EB	46.16	64.01	70	70
FatBlood	Xylene - p	E	Gargas *et al.*, 1989	PB	46.16	44.31	794	794
FatBlood	Xylene - p	H	Meulenberg and Vijverberg, 2000	EB	46.16	53.45	-62	62
FatBlood	Xylene - p	H	Meulenberg and Vijverberg, 2000	PB	46.16	96.65	616	616
FatBlood	Xylene - p	P	Poulin and Krishnan, 1995b	D	46.16	1.56	402	402
FatBlood	Xylene - p	P	Poulin and Krishnan, 1996a	EB	46.16	51.44	-27	27
FatBlood	Xylene - p	P	Poulin and Krishnan, 1996a	PB	46.16	342.07	326	326
Kidney:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	EB	1.73	5.78	-22	22
Kidney:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	PB	1.73	11.94	26	26
Live:Blood	Ethyl benzene	H	DeJongh *et al.*, 1997	D	1.20	2.45	186	186
Live:Blood	Ethyl benzene	E	Gargas *et al.*, 1988	EB	1.20	1.58	-5	5
Live:Blood	Ethyl benzene	E	Gargas *et al.*, 1988	PB	1.20	1.88	100	100

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
Liver:Blood	Ethyl benzene	E	Gargas *et al.*, 1989	EB	1.20	2.78	80	80
Liver:Blood	Ethyl benzene	E	Gargas *et al.*, 1989	PB	1.20	2.08	405	405
Liver:Blood	Ethyl benzene	H	Meulenberg and Vijverberg, 2000	EB	1.20	2.31	38	38
Liver:Blood	Ethyl benzene	H	Meulenberg and Vijverberg, 2000	PB	1.20	4.41	6	6
Liver:Blood	Ethyl benzene	P	Poulin and Krishnan, 1995b	D	1.20	1.10	5	5
Liver:Blood	Ethyl benzene	P	Poulin and Krishnan, 1996a	EB	1.20	2.31	-5	5
Liver:Blood	Ethyl benzene	P	Poulin and Krishnan, 1996a	PB	1.20	17.23	-24	24
Liver:Blood	Nonane	H	DeJongh *et al.*, 1997	D	1.29	6.64	408	408
Liver:Blood	Nonane	P	Poulin and Krishnan, 1995b	D	1.29	1.10	-30	30
Liver:Blood	Toluene	H	DeJongh *et al.*, 1997	D	4.64	1.89	306	306
Liver:Blood	Toluene	E	Gargas *et al.*, 1988	EB	4.64	1.96	-28	28
Liver:Blood	Toluene	E	Gargas *et al.*, 1988	PB	4.64	1.50	-97	97
Liver:Blood	Toluene	E	Gargas *et al.*, 1989	EB	4.64	2.76	96	96
Liver:Blood	Toluene	E	Gargas *et al.*, 1989	PB	4.64	1.60	813	813
Liver:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	EB	4.64	1.75	-9	9
Liver:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	PB	4.64	3.62	25	25
Liver:Blood	Toluene	P	Poulin and Krishnan, 1995b	D	4.64	1.10	-54	54
Liver:Blood	Toluene	P	Poulin and Krishnan, 1996a	EB	4.64	2.60	77	77
Liver:Blood	Toluene	P	Poulin and Krishnan, 1996a	PB	4.64	12.64	-40	40

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
Liver:Blood	Xylene - m	H	DeJongh *et al.*, 1997	D	1.84	2.53	634	634
Liver:Blood	Xylene - m	E	Gargas *et al.*, 1988	EB	1.84	1.68	-17	17
Liver:Blood	Xylene - m	E	Gargas *et al.*, 1988	PB	1.84	1.83	23	23
Liver:Blood	Xylene - m	E	Gargas *et al.*, 1989	EB	1.84	2.91	39	39
Liver:Blood	Xylene - m	E	Gargas *et al.*, 1989	PB	1.84	2.03	104	104
Liver:Blood	Xylene - m	H	Meulenberg and Vijverberg, 2000	EB	1.84	2.36	0	0
Liver:Blood	Xylene - m	H	Meulenberg and Vijverberg, 2000	PB	1.84	4.37	126	126
Liver:Blood	Xylene - m	P	Poulin and Krishnan, 1995b	D	1.84	1.10	-46	46
Liver:Blood	Xylene - m	P	Poulin and Krishnan, 1996a	EB	1.84	2.99	1	1
Liver:Blood	Xylene - m	P	Poulin and Krishnan, 1996a	PB	1.84	17.67	-35	35
Liver:Blood	Xylene - o	H	DeJongh *et al.*, 1997	D	2.37	2.41	118	118
Liver:Blood	Xylene - o	E	Gargas *et al.*, 1988	EB	2.37	1.85	-52	52
Liver:Blood	Xylene - o	E	Gargas *et al.*, 1988	PB	2.37	1.72	628	628
Liver:Blood	Xylene - o	E	Gargas *et al.*, 1989	EB	2.37	3.04	-4	4
Liver:Blood	Xylene - o	E	Gargas *et al.*, 1989	PB	2.37	1.90	31	31
Liver:Blood	Xylene - o	H	Meulenberg and Vijverberg, 2000	EB	2.37	2.42	58	58
Liver:Blood	Xylene - o	H	Meulenberg and Vijverberg, 2000	PB	2.37	4.30	-43	43
Liver:Blood	Xylene - o	P	Poulin and Krishnan, 1995b	D	2.37	1.10	-58	58
Liver:Blood	Xylene - o	P	Poulin and Krishnan, 1996a	EB	2.37	3.38	-9	9
Liver:Blood	Xylene - o	P	Poulin and Krishnan, 1996a	PB	2.37	16.96	-5	5
Liver:Blood	Xylene - p	H	DeJongh *et al.*, 1997	D	1.94	2.45	120	120
Liver:Blood	Xylene - p	E	Gargas *et al.*, 1988	EB	1.94	1.70	-36	36

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
Liver:Blood	Xylene - p	E	Gargas *et al.*, 1988	PB	1.94	1.86	34	34
Liver:Blood	Xylene - p	E	Gargas *et al.*, 1989	EB	1.94	2.98	16	16
Liver:Blood	Xylene - p	E	Gargas *et al.*, 1989	PB	1.94	2.06	56	56
Liver:Blood	Xylene - p	H	Meulenberg and Vijverberg, 2000	EB	1.94	2.43	11	11
Liver:Blood	Xylene - p	H	Meulenberg and Vijverberg, 2000	PB	1.94	4.39	34	34
Liver:Blood	Xylene - p	P	Poulin and Krishnan, 1995b	D	1.94	1.10	-32	32
Liver:Blood	Xylene - p	P	Poulin and Krishnan, 1996a	EB	1.94	2.59	437	437
Liver:Blood	Xylene - p	P	Poulin and Krishnan, 1996a	PB	1.94	17.23	-34	34
Musce:Blood	Ethyl benzene	H	DeJongh *et al.*, 1997	D	1.00	0.81	162	162
Musce:Blood	Ethyl benzene	E	Gargas *et al.*, 1988	EB	1.00	0.59	33	33
Musce:Blood	Ethyl benzene	E	Gargas *et al.*, 1988	PB	1.00	0.70	42	42
Musde:Blood	Ethyl benzene	E	Gargas *et al.*, 1989	EB	1.00	0.94	109	109
Musde:Blood	Ethyl benzene	E	Gargas *et al.*, 1989	PB	1.00	0.70	132	132
Musde:Blood	Ethyl benzene	H	Meulenberg and Vijverberg, 2000	EB	1.00	0.89	28	28
Musde:Blood	Ethyl benzene	H	Meulenberg and Vijverberg, 2000	PB	1.00	1.70	788	788
Musde:Blood	Ethyl benzene	P	Poulin and Krishnan, 1995b	D	1.00	0.97	-60	60
Musde:Blood	Ethyl benzene	P	Poulin and Krishnan, 1996a	EB	1.00	0.67	-31	31

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
Musce:Blood	Ethyl benzene	P	Poulin and Krishnan, 1996a	PB	1.00	5.02	-12	12
Musce:Blood	Nonane	H	DeJongh *et al.*, 1997	D	1.39	1.46	68	68
Musce:Blood	Nonane	P	Poulin and Krishnan, 1995b	D	1.39	0.97	-55	55
Musce:Blood	Toluene	H	DeJongh *et al.*, 1997	D	1.54	0.71	26	26
Musce:Blood	Toluene	E	Gargas *et al.*, 1988	EB	1.54	0.84	-97	97
Musde:Blood	Toluene	E	Gargas *et al.*, 1988	PB	1.54	0.64	32	32
Musde:Blood	Toluene	E	Gargas *et al.*, 1989	EB	1.54	1.05	-97	97
Musde:Blood	Toluene	E	Gargas *et al.*, 1989	PB	1.54	0.61	74	74
Musde:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	EB	1.54	0.69	138	138
Musde:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	PB	1.54	1.42	-19	19
Musde:Blood	Toluene	P	Poulin and Krishnan, 1995b	D	1.54	0.97	-8	8
Musde:Blood	Toluene	P	Poulin and Krishnan, 1996a	EB	1.54	0.80	-39	39
Musde:Blood	Toluene	P	Poulin and Krishnan, 1996a	PB	1.54	3.86	59	59
Musde:Blood	Xylene - m	H	DeJongh *et al.*, 1997	D	0.96	0.83	41	41
Musde:Blood	Xylene - m	E	Gargas *et al.*, 1988	EB	0.96	0.63	-8	8

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
Musde:Blood	Xylene - m	E	Gargas *et al.*, 1988	PB	0.96	0.69	9	9
Musde:Blood	Xylene - m	E	Gargas *et al.*, 1989	EB	0.96	0.99	11	11
Musde:Blood	Xylene - m	E	Gargas *et al.*, 1989	PB	0.96	0.69	92	92
Musde:Blood	Xylene - m	H	Meulenberg and Vijverberg, 2000	EB	0.96	0.91	-40	40
Musde:Blood	Xylene - m	H	Meulenberg and Vijverberg, 2000	PB	0.96	1.69	-41	41
Musde:Blood	Xylene - m	P	Poulin and Krishnan, 1995b	D	0.96	0.97	-37	37
Musde:Blood	Xylene - m	P	Poulin and Krishnan, 1996a	EB	0.96	0.87	-44	44
Musde:Blood	Xylene - m	P	Poulin and Krishnan, 1996a	PB	0.96	5.13	-9	9
Musde:Blood	Xylene - o	H	DeJongh *et al.*, 1997	D	1.16	0.81	171	171
Musde:Blood	Xylene - o	E	Gargas *et al.*, 1988	EB	1.16	0.71	348	348
Musde:Blood	Xylene - o	E	Gargas *et al.*, 1988	PB	1.16	0.65	-32	32
Musde:Blood	Xylene - o	E	Gargas *et al.*, 1989	EB	1.16	1.05	641	641
Musde:Blood	Xylene - o	E	Gargas *et al.*, 1989	PB	1.16	0.65	268	268
Musde:Blood	Xylene - o	H	Meulenberg and Vijverberg, 2000	EB	1.16	0.94	63	63
Musde:Blood	Xylene - o	H	Meulenberg and Vijverberg, 2000	PB	1.16	1.68	-30	30

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
Musce:Blood	Xylene - o	P	Poulin and Krishnan, 1995b	D	1.16	0.97	-48	48
Musce:Blood	Xylene - o	P	Poulin and Krishnan, 1996a	EB	1.16	0.99	-10	10
Musce:Blood	Xylene - o	P	Poulin and Krishnan, 1996a	PB	1.16	4.95	-29	29
Musce:Blood	Xylene - p	H	DeJongh *et al.*, 1997	D	1.06	0.81	-96	96
Musde:Blood	Xylene - p	E	Gargas *et al.*, 1988	EB	1.06	0.64	71	71
Musde:Blood	Xylene - p	E	Gargas *et al.*, 1988	PB	1.06	0.70	-7	7
Musde:Blood	Xylene - p	E	Gargas *et al.*, 1989	EB	1.06	1.01	235	235
Musde:Blood	Xylene - p	E	Gargas *et al.*, 1989	PB	1.06	0.70	-8	8
Musde:Blood	Xylene - p	H	Meulenberg and Vijverberg, 2000	EB	1.06	0.94	861	861
Musde:Blood	Xylene - p	H	Meulenberg and Vijverberg, 2000	PB	1.06	1.69	-6	6
Musde:Blood	Xylene - p	P	Poulin and Krishnan, 1995b	D	1.06	0.97	151	151
Musde:Blood	Xylene - p	P	Poulin and Krishnan, 1996a	EB	1.06	0.75	-44	44
Musde:Blood	Xylene - p	P	Poulin and Krishnan, 1996a	PB	1.06	5.02	371	371

Table B-2. Results of Algorithms for Human Blood:Air and Tissue:Blood (Direct, PC_{EB} and PC_{PB}) PC Values

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
Blood:Air	Ethyl benzene	E	Abraham *et al.*, 1985		28.40	15.11	-46.81	47
Blood:Air	Ethyl benzene	E	Gargas *et al.*, 1989		28.40	35.97	26.65	27
Blood:Air	Ethyl benzene	H	Meulenberg and Vijverberg, 2000		28.40	28.84	1.56	2
Blood:Air	Ethyl benzene	P	Poulin and Krishnan, 1996a		28.40	10.99	-61.32	61
Blood:Air	Ethyl benzene	E	Tichy, 1991		28.40	7.96	-71.98	72
Blood:Air	Toluene	E	Abraham *et al.*, 1985		14.30	11.28	-21.14	21
Blood:Air	Toluene	E	Gargas *et al.*, 1989		14.30	18.07	26.37	26
Blood:Air	Toluene	H	Meulenberg and Vijverberg, 2000		14.30	9.42	-34.12	34
Blood:Air	Toluene	P	Poulin and Krishnan, 1996a		14.30	5.93	-58.52	59
Blood:Air	Toluene	E	Tichy, 1991		14.30	7.31	-48.88	49
Blood:Air	Trimethyl benzene, 1,2,3-	E	Abraham *et al.*, 1985		66.50	29.12	-56.21	56
Blood:Air	Trimethyl benzene, 1,2,3-	E	Gargas *et al.*, 1989		66.50	77.90	17.15	17
Blood:Air	Trimethyl benzene, 1,2,3-	H	Meulenberg and Vijverberg, 2000		66.50	80.96	21.75	22
Blood:Air	Trimethyl benzene, 1,2,3-	P	Poulin and Krishnan, 1996a		66.50	52.41	-21.19	21
Blood:Air	Trimethyl benzene, 1,2,3-	E	Tichy, 1991		66.50	14.74	-77.84	78
Blood:Air	Trimethyl benzene, 1,2,4-	E	Abraham *et al.*, 1985		59.10	19.97	-66.21	66
Blood:Air	Trimethyl benzene, 1,2,4-	E	Gargas *et al.*, 1989		59.10	62.90	6.43	6
Blood:Air	Trimethyl benzene, 1,2,4-	H	Meulenberg and Vijverberg, 2000		59.10	74.92	26.76	27

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
Blood:Air	Trimethyl benzene, 1,2,4-	P	Poulin and Krishnan, 1996a		59.10	40.32	-31.77	32
Blood:Air	Trimethyl benzene, 1,2,4-	E	Tichy, 1991		59.10	9.11	-84.59	85
Blood:Air	Trimethyl benzene, 1,3,5-	E	Abraham *et al.*, 1985		43.00	16.48	-61.67	62
Blood:Air	Trimethyl benzene, 1,3,5-	E	Gargas *et al.*, 1989		43.00	56.47	31.32	31
Blood:Air	Trimethyl benzene, 1,3,5-	H	Meulenberg and Vijverberg, 2000		43.00	72.27	68.07	68
Blood:Air	Trimethyl benzene, 1,3,5-	P	Poulin and Krishnan, 1996a		43.00	14.02	-67.40	67
Blood:Air	Trimethyl benzene, 1,3,5-	E	Tichy, 1991		43.00	7.13	-83.42	83
Blood:Air	Xylene - m	E	Abraham *et al.*, 1985		32.20	15.37	-52.26	52
Blood:Air	Xylene - m	E	Gargas *et al.*, 1989		32.20	35.25	9.47	9
Blood:Air	Xylene - m	H	Meulenberg and Vijverberg, 2000		32.20	27.15	-15.68	16
Blood:Air	Xylene - m	P	Poulin and Krishnan, 1996a		32.20	12.88	-60.01	60
Blood:Air	Xylene - m	E	Tichy, 1991		32.20	8.27	-74.31	74
Blood:Air	Xylene - o	E	Abraham *et al.*, 1985		35.05	20.67	-41.02	41
Blood:Air	Xylene - o	E	Gargas *et al.*, 1989		35.05	42.70	21.82	22
Blood:Air	Xylene - o	H	Meulenberg and Vijverberg, 2000		35.05	30.82	-12.07	12
Blood:Air	Xylene - o	P	Poulin and Krishnan, 1996a		35.05	16.16	-53.90	54
Blood:Air	Xylene - o	E	Tichy, 1991		35.05	11.92	-66.00	66
Blood:Air	Xylene - p	E	Abraham *et al.*, 1985		41.85	14.62	-65.06	65
Blood:Air	Xylene - p	E	Gargas *et al.*, 1989		41.85	34.24	-18.19	18
Blood:Air	Xylene - p	H	Meulenberg and Vijverberg, 2000		41.85	26.78	-36.02	36
Blood:Air	Xylene - p	P	Poulin and Krishnan, 1996a		41.85	10.86	-74.06	74

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
Blood:Air	Xylene - p	E	Tichy, 1991		41.85	7.76	-81.45	81
Brain:Blood	Toluene	E	Abraham *et al.*, 1985	EB	3.53	1.91	-46	46
Brain:Blood	Toluene	E	Abraham *et al.*, 1985	PB	3.53	1.50	-57	57
Brain:Blood	Toluene	H	Balaz and Lukacova, 1999	D	3.53	2.85	-19	19
Brain:Blood	Toluene	H	DeJongh *et al.*, 1997	D	3.53	3.17	-10	10
Brain:Blood	Toluene	E	Fiserova-Bergerova and Diaz, 1986	D	3.53	3.23	-8	8
Brain:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	EB	3.53	1.60	-55	55
Brain:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	PB	3.53	2.42	-31	31
Brain:Blood	Toluene	E	Tichy, 1991	EB	3.53	2.34	-34	34
Brain:Blood	Toluene	E	Tichy, 1991	PB	3.53	2.78	-21	21
Fat:Blood	Ethyl benzene	E	Abraham *et al.*, 1985	EB	62.11	87.83	41	41
Fat:Blood	Ethyl benzene	E	Abraham *et al.*, 1985	PB	62.11	165.13	166	166
Fat:Blood	Ethyl benzene	H	Balaz and Lukacova, 1999	D	62.11	24.19	-61	61
Fat:Blood	Ethyl benzene	H	DeJongh *et al.*, 1997	D	62.11	105.38	70	70
Fat:Blood	Ethyl benzene	H	Meulenberg and Vijverberg, 2000	EB	62.11	59.90	-4	4
Fat:Blood	Ethyl benzene	H	Meulenberg and Vijverberg, 2000	PB	62.11	58.99	-5	5
Fat:Blood	Ethyl benzene	P	Poulin and Krishnan, 1996a	EB	62.11	67.14	8	8
Fat:Blood	Ethyl benzene	P	Poulin and Krishnan, 1996a	PB	62.11	173.57	179	179
Fat:Blood	Ethyl benzene	E	Tichy, 1991	EB	62.11	66.54	7	7
Fat:Blood	Ethyl benzene	E	Tichy, 1991	PB	62.11	237.48	282	282
Fat:Blood	Toluene	E	Abraham *et al.*, 1985	EB	72.98	56.73	-22	22
Fat:Blood	Toluene	E	Abraham *et al.*, 1985	PB	72.98	71.94	-1	1
Fat:Blood	Toluene	H	Balaz and Lukacova, 1999	D	72.98	18.09	-75	75
Fat:Blood	Toluene	H	DeJongh *et al.*, 1997	D	72.98	93.43	28	28

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
Fat:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	EB	72.98	33.48	-54	54
Fat:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	PB	72.98	50.82	-30	30
Fat:Blood	Toluene	P	Poulin and Krishnan, 1996a	EB	72.98	59.70	-18	18
Fat:Blood	Toluene	P	Poulin and Krishnan, 1996a	PB	72.98	143.94	97	97
Fat:Blood	Toluene	E	Tichy, 1991	EB	72.98	50.26	-31	31
Fat:Blood	Toluene	E	Tichy, 1991	PB	72.98	98.32	35	35
Fat:Blood	Xylene - m	E	Abraham *et al.*, 1985	EB	60.16	73.23	22	22
Fat:Blood	Xylene - m	E	Abraham *et al.*, 1985	PB	60.16	153.38	155	155
Fat:Blood	Xylene - m	H	Balaz and Lukacova, 1999	D	60.16	24.78	-59	59
Fat:Blood	Xylene - m	H	DeJongh *et al.*, 1997	D	60.16	106.27	77	77
Fat:Blood	Xylene - m	H	Meulenberg and Vijverberg, 2000	EB	60.16	49.40	-18	18
Fat:Blood	Xylene - m	H	Meulenberg and Vijverberg, 2000	PB	60.16	58.59	-3	3
Fat:Blood	Xylene - m	P	Poulin and Krishnan, 1996a	EB	60.16	70.37	17	17
Fat:Blood	Xylene - m	P	Poulin and Krishnan, 1996a	PB	60.16	175.98	193	193
Fat:Blood	Xylene - m	E	Tichy, 1991	EB	60.16	56.31	-6	6
Fat:Blood	Xylene - m	E	Tichy, 1991	PB	60.16	219.18	264	264
Fat:Blood	Xylene - o	E	Abraham *et al.*, 1985	EB	69.89	75.85	9	9
Fat:Blood	Xylene - o	E	Abraham *et al.*, 1985	PB	69.89	128.60	84	84
Fat:Blood	Xylene - o	H	Balaz and Lukacova, 1999	D	69.89	23.83	-66	66
Fat:Blood	Xylene - o	H	DeJongh *et al.*, 1997	D	69.89	104.80	50	50
Fat:Blood	Xylene - o	H	Meulenberg and Vijverberg, 2000	EB	69.89	50.53	-28	28
Fat:Blood	Xylene - o	H	Meulenberg and Vijverberg, 2000	PB	69.89	57.47	-18	18
Fat:Blood	Xylene - o	P	Poulin and Krishnan, 1996a	EB	69.89	79.31	13	13
Fat:Blood	Xylene - o	P	Poulin and Krishnan, 1996a	PB	69.89	172.01	146	146

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
Fat:Blood	Xylene - o	E	Tichy, 1991	EB	69.89	60.86	-13	13
Fat:Blood	Xylene - o	E	Tichy, 1991	PB	69.89	179.01	156	156
Fat:Blood	Xylene - p	E	Abraham *et al.*, 1985	EB	51.77	55.58	7	7
Fat:Blood	Xylene - p	E	Abraham *et al.*, 1985	PB	51.77	159.08	207	207
Fat:Blood	Xylene - p	H	Balaz and Lukacova, 1999	D	51.77	24.19	-53	53
Fat:Blood	Xylene - p	H	DeJongh *et al.*, 1997	D	51.77	105.38	104	104
Fat:Blood	Xylene - p	H	Meulenberg and Vijverberg, 2000	EB	51.77	37.61	-27	27
Fat:Blood	Xylene - p	H	Meulenberg and Vijverberg, 2000	PB	51.77	58.79	14	14
Fat:Blood	Xylene - p	P	Poulin and Krishnan, 1996a	EB	51.77	45.02	-13	13
Fat:Blood	Xylene - p	P	Poulin and Krishnan, 1996a	PB	51.77	173.57	235	235
Fat:Blood	Xylene - p	E	Tichy, 1991	EB	51.77	42.38	-18	18
Fat:Blood	Xylene - p	E	Tichy, 1991	PB	51.77	228.45	341	341
Heart:Blood	Toluene	H	Balaz and Lukacova, 1999	D	2.01	2.43	21	21
Kidney:Blood	Toluene	E	Abraham *et al.*, 1985	EB	1.73	0.89	-49	49
Kidney:Blood	Toluene	E	Abraham *et al.*, 1985	PB	1.73	1.13	-35	35
Kidney:Blood	Toluene	H	Balaz and Lukacova, 1999	D	1.73	1.50	-13	13
Kidney:Blood	Toluene	H	DeJongh *et al.*, 1997	D	1.73	2.30	33	33
Kidney:Blood	Toluene	E	Fiserova-Bergerova and Diaz, 1986	D	1.73	2.18	26	26
Kidney:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	EB	1.73	0.92	-47	47
Kidney:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	PB	1.73	1.39	-20	20
Kidney:Blood	Toluene	E	Tichy, 1991	EB	1.73	1.08	-37	37
Kidney:Blood	Toluene	E	Tichy, 1991	PB	1.73	2.12	23	23
Liver:Blood	Toluene	E	Abraham *et al.*, 1985	EB	4.68	1.29	-73	73
Liver:Blood	Toluene	E	Abraham *et al.*, 1985	PB	4.68	1.63	-65	65
Liver:Blood	Toluene	H	Balaz and Lukacova, 1999	D	4.68	2.78	-40	40

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
Liver:Blooc	Toluene	H	DeJongh *et al.*, 1997	D	4.68	5.05	8	8
Liver:Blooc	Toluene	E	Fiserova-Bergerova and Diaz, 1986	D	4.68	3.68	-21	21
Liver:Blooc	Toluene	P	Poulin and Krishnan, 1996a	EB	4.68	3.65	-22	22
Liver:Blooc	Toluene	P	Poulin and Krishnan, 1996a	PB	4.68	8.79	88	88
Liver:Blooc	Toluene	E	Tichy, 1991	EB	4.68	2.44	-48	48
Liver:Blooc	Toluene	E	Tichy, 1991	PB	4.68	4.76	2	2
Liver:Blooc	Xylene - m	E	Abraham *et al.*, 1985	EB	3.02	0.99	-67	67
Liver:Blooc	Xylene - m	E	Abraham *et al.*, 1985	PB	3.02	2.07	-31	31
Liver:Blooc	Xylene - m	H	Balaz and Lukacova, 1999	D	3.02	4.04	34	34
Liver:Blooc	Xylene - m	H	DeJongh *et al.*, 1997	D	3.02	6.71	122	122
Liver:Blooc	Xylene - m	E	Fiserova-Bergerova and Diaz, 1986	D	3.02	3.13	4	4
Liver:Blooc	Xylene - m	P	Poulin and Krishnan, 1996a	EB	3.02	4.22	40	40
Liver:Blooc	Xylene - m	P	Poulin and Krishnan, 1996a	PB	3.02	10.55	249	249
Liver:Blooc	Xylene - m	E	Tichy, 1991	EB	3.02	2.62	-13	13
Liver:Blood	Xylene - m	E	Tichy, 1991	PB	3.02	10.19	237	237
Lung:Blood	Toluene	E	Abraham *et al.*, 1985	EB	2.03	0.31	-85	85
Lung:Blood	Toluene	E	Abraham *et al.*, 1985	PB	2.03	0.39	-81	81
Lung:Blood	Toluene	H	Balaz and Lukacova, 1999	D	2.03	1.01	-50	50
Lung:Blood	Toluene	E	Fiserova-Bergerova and Diaz, 1986	D	2.03	1.41	-31	31
Lung:Blood	Toluene	E	Tichy, 1991	EB	2.03	0.76	-63	63
Lung:Blood	Toluene	E	Tichy, 1991	PB	2.03	1.49	-27	27
Muscle:Blood	Toluene	E	Abraham *et al.*, 1985	EB	3.39	1.08	-68	68
Muscle:Blood	Toluene	E	Abraham *et al.*, 1985	PB	3.39	1.37	-60	60
Muscle:Blood	Toluene	H	Balaz and Lukacova, 1999	D	3.39	2.07	-39	39
Muscle:Blood	Toluene	H	DeJongh *et al.*, 1997	D	3.39	3.28	-3	3
Muscle:Blood	Toluene	E	Fiserova-Bergerova and Diaz, 1986	D	3.39	2.83	-16	16

Tissue	Chemical	Equation Type (Empirical, Hybrid, Physiological)	Source	Tissue:Blood Calculation (Direct, PC_{EB}, PC_{PB})	Experimental Value	Calculated Value	Percent Error	Absolute Percent Error
Muscle:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	EB	3.39	1.15	-66	66
Muscle:Blood	Toluene	H	Meulenberg and Vijverberg, 2000	PB	3.39	1.75	-48	48
Muscle:Blood	Toluene	P	Poulin and Krishnan, 1996a	EB	3.39	2.95	-13	13
Muscle:Blood	Toluene	P	Poulin and Krishnan, 1996a	PB	3.39	7.10	110	110